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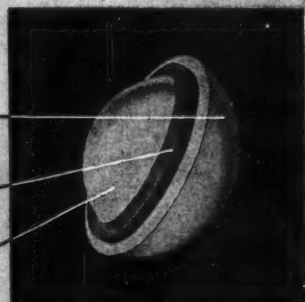
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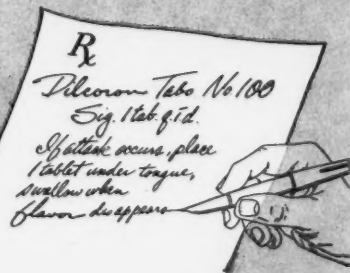
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Editorial

Grandeur and Poverty of Medical Specialization

Aspiration Toward a New Humanism

THE outstanding progress of contemporary medicine is not free of perils. The profound scientific and technical transformation of medicine constitutes one of the crucial problems of our time. This is why Professor Rijlant, illustrious President of the III World Congress of Cardiology, asked me to discuss this problem and its immediate consequence, the pre-eminence of specialization, fertile in valuable achievements, but also pregnant with risks.

THE DANGERS OF SPECIALIZATION

It is true that specialization carries within itself an enormous expansive force of progress, responsible in great part for the spectacular advance which we are witnessing, but it also contains the germ of regression in the intellectual and spiritual realm. Specialization means fragmentation, partial vision, limitation of our horizon. What is gained in depth is lost in breadth. In order to master one field of knowledge one must abandon the rest; man thus confines himself to one point and sacrifices the whole vision of his science and the universal vision of his world. With this his general culture suffers, for it must let go of much, as one who throws out ballast; then his scientific training suffers, for he

ceases to look on science as a whole in order to keep a poor little portion in his hands; finally his moral world suffers, for the sacrifice of culture constitutes a sacrifice of values which should set the standard of his life. And in this drama of the present-day scientist an imminent risk is foreshadowed, the dehumanization of medicine and the dehumanization of the physician.

One who looks only at the thundering race of the progress that medicine is achieving may not perceive the severe risks which that race brings with it. He may not be aware that we are at a crossroads, able to make ourselves change direction, and he may not realize that for these conquests and material advances we may all, perhaps, have to pay dearly—the physician, the patient, and medicine itself.

This is a real problem, not a fictitious one. It constitutes one of the great preoccupations of the physicians, educators, and philosophers of our time. On more than one occasion I have expressed my acute anxiety over this situation, which was unknown to our ancestors. As I am neither philosopher nor historian, I am aware of my slight competence to take up this matter, but since the problem touches me as physician and educator, I have accepted the invitation and I wish to present to you a series of reflections that aim to awake the interest of all, old and young. Above all, I feel it important to address myself to the young,

From the National Institute of Cardiology, National University of Mexico, Mexico, D. F.

General Lecture presented before the Third World Congress of Cardiology, Brussels, September 1958.

for they are those who will shape the medicine of the future and upon them depends the stamp they will impress upon it as a science, and the form of medicine which they will practice tomorrow as a profession.

I know very well that a long exposition of general ideas is not to the taste of our age, and that physicians usually prefer concrete contributions, new facts, daring technics, or mathematical formulations that define unsolved problems. I understand this attitude; basically all that is beautiful. To conquer a new truth is like seizing a star. Moreover, it gives the feeling of power or the intoxication of triumph, both of which suit the spirit of youth. In spite of that, I suggest that we imagine ourselves students of Hellenic times and walk together through the gardens of Academe or the Lyceum while we discuss serenely some general matters of medicine.

PRE-EMINENCE OF SCIENTIFIC MEDICINE

That we are at a fascinating moment of the evolution of medicine is something that even the uninitiated observe: the advances achieved in this first half of our century are worth as much as all that was accumulated in many preceding centuries. Of course this prodigious advance could not have been attained without the work of those who preceded us. Present science already existed in the germ of the previous work; but the miracle of the seed does not at all lessen the majesty of the tree.

It was in this century that medicine ceased to be purely clinical, and anatomic comparison was no longer enough. A day came when detailed studies of organic function were required. To achieve them, physics and chemistry, biology and mathematics entered medicine, first timidly and then tumultuously, and with them came complex technics, precision instruments, and the rigors of mathematical analysis. It was the heyday of the laboratory and the beginning of a new era, the era of research. The so-called basic sciences came to change the traditional aspect of medicine, attempting to substitute scientific for empirical knowledge, and laboratory experiment for pure observation.

It is impossible to trace the exact limit that separates the two epochs. Never in history has it been possible to say where one age ends and another begins, and one must accept conventional boundaries. Even in the most radical changes, the ages superimpose or overlap, as happened with medieval and Renaissance medicine, when Galen continued to reign in physiology a century after Vesalius had begun his revolution in anatomy. If this happens in ages which are essentially opposed, as the medieval with its scholastic philosophy that became dogma, and the Renaissance with its scientific criterion that became free criticism, even greater difficulty exists in tracing the starting point of the scientific and experimental medicine of our day.

The fact is that basically the difference is not essential but quantitative; medicine was already scientific earlier, especially that of the nineteenth century. One cannot ask for greater scientific exactness than that of Laennec's comparisons or of Claude Bernard's experiments. Science could not be more precise than it was in the hands of Pasteur, of Koch, and of Virchow, nor was it ever more disinterested and accurate than in Roentgen's experiments. It is not then, that our medicine is scientific and the other was not. The change comes rather from the fact that now it is not only a fragmentary aspect or an isolated field that is being transformed; all the fields of medicine are being attacked scientifically, all are being subjected to experimental methods, and in all, the basic sciences have entered to clarify problems.

GREAT CONTRIBUTIONS OF OUR TIME

No one could deny that the harvest has been extraordinary, not to say fantastic. If we limit ourselves solely to our field of cardiology, we see that in this half century cardiovascular radiology has been born and has attained the technical refinements of kymography, tomography, selective angiocardiology, and radiocinematography. Electrocardiography has been born, with its immense contribution, particularly in the field of coronary insufficiency and mechanical behavior.

ie to hypertrophies or overloading. The second exploration of cardiac catheterization has been born, with all that it teaches with regard to pressures, output and flow, tissue respiration and metabolism. We see that almost all that is known of congenital, hypertensive, and pulmonary cardiopathies belongs to our epoch, as well as the knowledge of myocardial infarction, deficiency, and Chagas cardiopathies. We see that with us has been born the surgery of the heart, the mastery over cardio-aortic syphilis and bacterial endocarditis, the control of sustained rheumatic activity and the prevention of rheumatic carditis by means of antibiotics; that our arsenal has been enriched with Fraenkel's atropine, Arnaud's ouabaine, Stohl's lanatosides, and all the gamut of hypotensive drugs, mercurial diuretics, vitamins, anticoagulant and antiarrhythmic medication. Why continue an interminable enumeration? The list would include the influence of hormones, the action of enzymes, and the role of electrolytes, all that world of new knowledge which has come to clarify causes and mechanisms in the chapter of diagnosis, and which has endowed us with effective arms in treatment and prevention.

Let the present-day contribution be placed on one side of the scales and on the other the contribution of the 50 preceding centuries, and it will be seen that there is no error in affirming that the recent harvest is superior to the old. If today one of the great cardiologists of the last century, Traube, Stokes, or Potain should come here to a Congress, his astonishment would know no bounds. He would begin by not understanding our technical language. What they could not even glimpse with all their wisdom and experience has today become an easy notion, within the grasp of any medical student.

SCIENTIFIC RESEARCH UNDER WAY

Their amazement at what has been accomplished in 2 or 3 generations would be infinitely greater if they gazed on what is being forged. The visceral pathology that they knew is beginning to be explained in terms of tis-

sue pathology and then of cell pathology; as well as being specific entities, diseases are turning into systemic reactions; in the background of rheumatic fever appears the reaction of fibroblastic tissue; instead of single causes—germ, toxic product or deficiency—complex interactions, allergic shocks, and enzyme actions reveal themselves; behind the organic lesions appear metabolic disturbances, profound biochemical changes or alteration of the physical properties of a cell or a membrane which change its electric charge, its salt interchange, or its richness in ions. When we reach the level of the atom, matter and energy are confused; the limit between the organic and the functional becomes blurred, and all the immense machine of the organism displays suffering even in its cells and its electrons when a disease sets in. To the astonishment of our visitors would be added the pleasure of seeing that their hypotheses now have validity as theories.

We who are present at these changes also see the progress with delight, but we begin to look with distress at what might be the medicine of tomorrow, the day when the investigations that are being carried on give out their answer. As in the dreams of the alchemists, we should not know what to do with such a medicine, transmuted and dehumanized, converted into a philosopher's stone.

THE ADVENT OF SPECIALTIES—PURE RESEARCH VERSUS CLINICAL RESEARCH

The natural result of this impressive mass of knowledge and of this technicalization of medicine, of this invasion of the physical, chemical and mathematical sciences, has been the birth of specialties. It is now impossible for one man to know, even in its essential aspects, all this world of medicine. It is impossible for him to follow its rapid transformation; impossible, too, for him to master all the techniques of study, so varied and so complex. As a sign of the times, specialties have sprung up, which permit a man to concentrate on one field and study it thoroughly until he masters it. What was an effect of the vertig-

inous advance of science became afterward a causal factor of that progress.

The advantage of medical specialization can no longer be debated, either in the pragmatic aspect of the profession or as a factor for the advance of knowledge. Each specialty has carried out clinical investigation in its field and all may glory in having furnished a great mass of contributions.

A specialist's research, however, is soon exhausted if he works only as a clinician and technician, without having basic scientific training. The great answers will be formulated in the language of physics, chemistry, and biology, supported by mathematical rigor. A conflict has arisen which appears more clearly each day, that of pure or basic research as opposed to applied clinical research. The "pure" scientists look on this latter with disdain as pragmatic and limited in its scope, and they even deny it the rank of science, claiming that it does not go much beyond empiric knowledge.

This is a grave error, which inhibits the collaboration between the two groups. Applied research may be as scientific as the other, though the two differ in their goals and their immediate results. It is true that disinterested research is that which usually gives the clue to the great scientific problems. It is true that Einstein's relativity theory made possible the study of atomic radiation and provided the basis for medication by radioactive isotopes, that Fleming's discovery made possible the manufacture of antibiotics and solved the treatment of infectious diseases, and that Planck's quantum theory is the truth which must some day explain the processes of oxidation in cell life and the transformation of chemical energy into electrical,—the basis of nervous activity,—or into mechanical,—the basis of muscular activity. But research applied to clinical medicine, though it is usually modest, is not therefore less noble, provided it is carried out with scientific method. The regulated experiment in the laboratory animal cannot be compared to the natural experiment provoked in man by disease. As long as the clinical investigator takes into consideration

the numerous variables and does not fall into false schematizations, he can achieve experimentation as rigorous as that of the laboratory and of the same scientific value.

As proof of the foregoing, there are the extraordinary contributions which we owe to clinical investigation. Mellanby rightly asked what we should know of vitamins B₁, C or D of insulin, thyroxin, and of the active principles of the liver and the stomach in pernicious anemia if experimentation had not been carried out by clinicians in the field of pathology.

One must then, react against the tendency observed in the younger generations to consider only laboratory investigation scientific and to look with disdain on clinical research as if it were a kind of secondary value. It is one of the many fetishes that the man of study creates, forgetting that the scientific quality does not depend on the tools that are used, but rather on the method which is followed, and that merit does not rest on the method, however scientific it may be, but on the creative idea. There is much laboratory research which is worth nothing because it is empty of content. Simmel has made the accusation that we have suffered for some time from a fetishist cult of method and we consider any contribution very valuable because of the simple fact that the method is impeccable, and there are even studies that justify the caustic phrase of Chesterton, that "much research reminds one of a blind man looking in a dark room for a black hat that is not there."

In reality, the two kinds of research are not strangers, and should, on the contrary, complement each other. Studies in the field of the normal may be made at the same time as those in the field of pathology; observation mates well with experimentation, and the contributions of analysis are solely the necessary stage by which to arrive at the work of synthesis.

SCIENTIFIC TRAINING OF THE SPECIALIST

For the specialists, cardiologists in our case, however, to be able to participate in this joint movement, they must have a sound scientific training. This should be an indispensable requisite today. It is no longer enough to be

good clinicians in the traditional sense of the word. That may be well for the practical ends of the profession but the cardiology of today is too much inlaid with exact sciences to be mastered without a solid scientific foundation. "You cannot become so much as a modest engineer here until you have first done the mathematics and the physics from which any true understanding of science must spring. You cannot be a specialist until you are a scientist," said Jacob Bronowsky to his students. We should say exactly the same today to those who wish to specialize in our field. *You cannot be specialists in Cardiology if you are not at the same time clinicians and scientists."*

To know traditional clinical medicine, to master the usual technics, to be informed of current theories, this is enough to make a practical cardiologist, but not a specialist in cardiology. The former are clinicians in the noble sense of the word, but they are clinicians of circumscribed activity, of limited range, very useful in the social community, but less so in the scientific community. The true specialists, on the other hand, are those who can advance the knowledge in their field.

This requirement that the specialist be a scientist as well as a clinician does not imply any scorn for traditional clinical medicine. The place of the latter is different, very high and very noble. I have referred to the specialist fitted for investigation, but I do not seek to have all cardiologists consecrated to it. I think, like Sir John Parkinson, that in every first class hospital a place of honor beside the scientists should be kept for the superior clinicians, those who are just that, clinicians of knowledge and experience, in whose hands the finest traditions are preserved and the trust and safety of the patients repose. They too live their special science, which is to keep men alive. They know that with a certain dose of science, and another of experience, a man is saved.

SCIENCE VERSUS HUMANISM

When the requisite of two-fold training is fulfilled by the specialists, there will arise

even more seriously the problem already mentioned in relation to the great development of sciences: I speak of their divorce from humanism. And the more the specialist cultivates his scientific side, the greater will be the risk. There will appear in him the tendency to overspecialization, which threatens to destroy the criterion of unity in science and which will make imminent the divorce from humanism. There is no worse form of spiritual mutilation in a physician than the lack of humanistic culture. He who lacks it may be a great technician in his craft, may be a learned man in his science, but in all else he cannot but be a barbarian, wholly ignorant of that which gives human understanding and sets the values of the moral world. And that, in a cardiologist, is unforgivable.

Humanism is not a luxury, nor a refinement of scholars who have time to waste in frivolities disguised as spiritual satisfactions. Humanism means culture, understanding of man and his aspirations and miseries;—evaluation of what is good, what is beautiful, and what is just in life; the setting of the standards that rule our internal world; the eagerness to excel which leads us, in the philosopher's phrase, to "match life with thought." The pursuit of humanism will make us cultured. Science is something else; it makes us strong but not better. Therefore the more learned the physician is, the more cultured he should be.

The humanists of the Renaissance, sated with the barbarous world in which they lived socially and with the obscure intellectual world of the Middle Ages, produced the great movement of the liberation of conscience. They reascended the river of history to seek contact with Greek culture; they sought inspiration in the great classics of literature and philosophy and learned to free themselves from scholastic dogmatism, utilizing reason. They realized that the major interest of man is that of looking at man, in order to know and understand him. Their vision then attained the breadth of the world and they could proudly shout Terence's phrase: "*homo sum, humani nihil a me alienum puto.*"

The world then experienced a miraculous hour that will never again be repeated in history, for there will never again be the happy conjunction of circumstances that engendered it. In that miraculous hour, Leonardo da Vinci exemplifies the prodigy, showing what is "a man capable of whatever a human creature can do"; Copernicus makes our world descend from its geocentric throne and sends it spinning humbly in its orbit; Vesalius initiates the revolution of medicine against the authority of texts; Michael Angelo creates another world in the Sistine Chapel, and makes marble speak: "*parla e per che non parla?*"; America rises from the ocean, divined by Columbus; and Asia is sketched on the horizon, announced by Marco Polo and confirmed by Vasco da Gama; and the printing press, the great renewer, undertakes to diffuse throughout the world this marvelous conjunction of rebellions against medieval life and scholastic thought.

It was this splendid humanism which engendered our modern world, which in the intellectual realm launched us in search of truth, questioning nature herself; and in the artistic aspect inculcated in us the love of beauty, free from sin; which in the spiritual realm infused in us the aspiration to be universal men, and which, revindicated in the moral realm, our higher dignity as men.

HUMANISM AND MEDICINE

It is this precious heritage that has given the physician through the ages, his superior position and his authority over his patients, making him a counsellor and guide, not only a physician. His culture has permitted him the understanding of the human problem that is enclosed in each clinical case, and understanding means sympathy. The physician is not a mechanic who is to repair a sick organism as one repairs a machine that is out of order. He is a man who looks at another man, with eagerness to help, offering what he has, a little of science and a great deal of understanding and sympathy. Why should we let this fundamental human aspect be lost? It comes not from our science but from deeper roots,

from our culture, which sets us a duty, and from our sensibility, which translates, to paraphrase Peguy, an impulse of the soul toward goodness.

It is useless for the skeptic to smile. He thinks that with his technic and his science he needs nothing more to master cardiology but he will be incomplete, a cripple, if he is not also rich in culture, deeply impregnated with humanism, a humanism rooted before he reaches the University, continued through all his medical studies, and prolonged afterward indefinitely throughout his whole life.

The skeptic's smile might perhaps be justified if it were argued that the scientist and the humanist adopt at times opposed and in a way antithetic positions—the humanist with his face turned toward the remote past, the scientist living solely in the present minute, avid of the latest finding, uninterested in the already surpassed knowledge of yesterday. These extreme situations fortunately are not the rule. The scientist who proceeded thus would prove that he does not deserve the name if he does not know that the science of today lacks foundation and meaning without that of yesterday, for it, according to the expression of Sartre, "is the only human activity which is truly cumulative and progressive." No, fortunately, these two conquests of man, science and culture, are neither opposed nor mutually exclusive; rather, they fraternize and complete each other harmoniously when man joins talent and sensibility.

THE HUMANISM OF OUR AGE

Faced by this situation, we may properly ask what is the humanism that is commended as a complement to scientific education. Is it classical humanism, that which cultivates the dead languages, glosses the Greek and Latin classics, and probes the history of philosophical thought?

It is not that, certainly. It would be a beautiful ideal if scientists could attain such a refinement of culture, recreating the archetype of the universal man. That has become impossible in our vertiginous age. There no longer exists the omnivalent man of that stat-

re, such as was Leonardo, who with equal competence prepared a *Treatise of Anatomy* in 30 volumes, painted the *Last Supper*, or worked out calculations so that man could fly, or such as were Alberti, Fraacastoro, or Erasmus or so many others who could equally well hold a chair of medicine or one of languages or one of philosophy.

Our age no longer permits such omnivariance. The humanism we pursue is not the traditional nostalgic one, as Lain Entralgo calls it, that looks only backward. There is room for a humanism of our time, dynamic and effective. "In the Beginning was the Word," says the Holy Gospel. It is the same in our case; the root of present humanism must be the knowledge of the principal living languages. Through them we shall be able to look at the thought of races and countries which are not ours and drink information at the very springs. We shall receive in passing the lesson in humility that science and culture do not end at the boundaries of our country. The whole world seethes, the whole world works and creates. How should we go on, in isolation, ignorant of ourselves, at once owners and prisoners of our own language? For scientific ends this constitutes a limitation of ignorance, and for human ends, it pushes us toward incomprehension, the first form of scorn. Already in the middle of the eighteenth century Sénac protested: "National prejudice," he said, "dominates even the scientists; many imagine that genius and knowledge are exclusive to their country and that the other nations are condemned by nature to sterility. This vanity may perhaps be useful to the States," he added, "but it is something that degrades the spirit." Because of all this I think that in the world of intelligence one's own language does not suffice and if a scientist is to be cultured, he should begin by cultivating languages.

Since it is an eternal aspiration, culture is not a universal and static thing; it changes and shapes itself according to the time and the place. Hence the knowledge of history is an essential requisite for contemporary humanism, broad history, of peoples, of civiliza-

tion and of men's thought. We physicians are interested moreover, decisively, in the history of our specialty, which shows us the evolution of medical doctrines. Jacobi said to his students: "For as without the knowledge of the history of your country you can not understand its structure, or without that of the embryo the full development of the body, so without that of your science and art you will not be a citizen in your profession."

In compliance with the duty imposed by culture, man must afterward immerse himself in the world in which he lives, feeling himself not a stranger, nor even a pure spectator of the social reality that surrounds him. He may be barely an atom of this world, if you wish, but alive and vibrant, a creative energy of his time; for one cannot conceive culture divorced from life itself, nor genuine humanism uninterested in the problems of man.

And when one has attained all this, the knowledge of languages and of history in its broadest sense, when one recognizes social reality and is interested in the hour in which one is living, the humanism of our age would be sad and dull if man did not adorn his spirit with selected readings, with frequent contact with the modern classics, with love of beauty—in word, music, or plastic art—and with reflection on the eternal themes of conduct—duty, love, goodness—all forms of sublimating the soul in the face of the hard reality of living. The march along these harsh paths of perfection leads up to a point, the same at which the classic humanists arrived, that of knowing that the highest concern of man must be man himself, in order to study and understand him, with all that this implies of interest in his life and respect for his creative effort.

This is the humanism which we must foment in our age, a humanism the deeper and more passionate, the greater the limitation imposed by an exigent and unilateral scientific education. This is the indispensable prescription for the specialist of today, that which teaches that what is important is not to know but to understand; to understand man, to understand the world, to understand one's position in life;

that which, moreover, aids him in developing the gift of sympathy with which he must approach the patient. As by a catalytic effect, humanism projected into science invites man to flee from selfish isolation and impells him to work nobly in collaboration at the same time as it offers him a formula to counteract, in large part, the harmful tendencies that rise from specialization—those of the scientist who isolates himself from other men, the specialty that separates itself from other specialties, the medicine which separates itself from other sciences, and the science which divorces itself from culture.

HUMANISM, A CORRECTIVE FOR SCIENTIFIC DEFORMITY

The situation of isolation and divorce is accentuated more each day. The younger generation seems not to have noticed it. I have been able to watch it at close quarters, because I have spent many years dedicated to the training of specialists in cardiology. In almost all of them one notes a passionate eagerness to master the technic rather than to possess themselves of the method, and the cult of the apparatus is more easily developed in them than a passion for scientific ideas. It is the characteristic error of our epoch which Samuel Ramos points out, that of raising the means to the rank of an end. "Before the marvelous results of technic," he says, "the scientist falls on his knees to her, forgetting that she is a simple means." On the other hand, general theories matter less to the young, and the problems of culture are wont to interest still less.

It is possible that the smile of the skeptic will appear again as he thinks that there is exaggeration in this, and that culture, though estimable, is more of an adornment than a necessity for the medical specialist. I, on the other hand, consider it as indispensable as scientific discipline itself, and because of this I say with complete conviction to all my students: *you cannot be good cardiologists as long as you are not cultured men*. This is a new way of repeating the old saying of Paracelsus in the sixteenth century: "It is a gross

thing for a physician to call himself a physician and find himself empty of philosophy and know nothing of it."

The humanist spirit imbued in the scientist obliges him to flee from pure pragmatism as a philosophy of medicine and forces him not to be content with facts without going deeply into their explanation, and not to let himself stick fast in accumulated data without seeking the theory which makes a whole of them. This attitude helps to clear up one of the great problems of our present medicine, which is fragmentary, disarticulated, rich in facts, and poor in theories. In earlier times there were too many theories and a lack of support by facts. Today when we have learned the lesson of "*saper vedere*," today we have an excess of facts and few general theories. Little analytical men abound and we lack superior men who can work out syntheses, whereas the true scientific spirit rests precisely upon alternating the two things. "Analytical investigations," says Sarton, "without synthetic attempts must necessarily degenerate into crude empiricism; synthetic constructions without periodic experimental contact must necessarily degenerate into a sterile dogmatism."

The humanistic spirit instilled into the scientist keeps him from reposing a mythical faith in science, or believing it to be of absolute value, and helps him to understand, humbly, its relativity, and to admit that science will never cover the entire field of medicine; that however great, however excessive its progress may be, there will always be a very broad field for the empiricism of knowledge, for the "chaste observation" of our ancestors. If all organic reactions could one day come to be measured, recorded, and even reproduced in the laboratory, there would always remain outside the rigorous control of physics and chemistry the psychic reactions of the patient, his sufferings and his anguish, as would the obscure genetic factor which has governed us since the beginning of time.

If it is not to be supposed that all this will fit within the rigidity of a mathematical formula, and if he who suffers is a man and not

machine or a laboratory retort, there will always be a place for the clinician to give voice to an opinion and lead medicine in the future as he has led it until now. Therefore he should not abandon his high human values and he should stubbornly enrich his culture. If because of the exigency of the age, his specialization turns toward pure science, his humanism will help him to bow with humility before the immensity of what he does not know. Shortly before his death, Newton, one of the giants of scientific thought, said sadly: "I do not know what I may appear to the world, but to myself I seem to have been only

like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."

I think it is time to stop. While we walked through the garden of Academe, discussing these general matters of medicine, the afternoon has ended. The sun has set beside the Pireus and there is only to be seen the brightness, half rose and half gold, of the sacred hill of the Acropolis. By good fortune this light is enough to guide our steps.

IGNACIO CHAVEZ



Pre-Harveian Doubts of Galenic Doctrine

Among our self-righteous forebears it was frequently the fashion to attach to the condemned man some indication or symbol of his crime, and in the case of Servetus, chained to the stake and about to be burned alive, a copy of his recently printed *Christianismi restitutio* was fastened to his leg. To Calvin it symbolized the heresies of the condemned man and Calvin's determination that they should be destroyed. That the book also contained the first printed description of the pulmonary circulation meant nothing to him. As a lawyer and theologian he would not have understood it, and as a believer in predestination and himself as one of "the choice elected few" it was of little consequence anyway. As a matter of fact, the entire edition of one thousand copies of the book was tracked down and almost completely destroyed so that to our knowledge only three copies have survived, but sufficient to gain for the author a recognition denied him in his own day. Thus the book which went with Servetus to his destruction and symbolized for Calvin the end of both the heretic and his heresies has, on the contrary, revived the name of the victim and for many has gained him a brighter place in history than that of his executioner. Finally, the fact that this first account of the pulmonary circulation is imbedded in a theological work is in the case of Servetus no cause for amazement.—CHARLES D. O'MALLEY. *The Complementary Careers of Michael Servetus: Theologian and Physician*. History of Medicine and Allied Sciences 8: 378, 1953.

Phonocardiographic Features of Atrial Septal Defect

By ROBERT EISENBERG, M.D., AND HERBERT N. HULTGREN, M.D.

The heart sounds of 20 patients with uncomplicated atrial septal defect have been analyzed, and the deviations from a normal control group were noted. Following complete closure of the defect 11 patients have been restudied, and the changes produced in the heart sounds by closure of the defect are discussed. By comparison of pre-operative and postoperative heart sounds and electrocardiograms it has been possible to ascribe some abnormalities of the heart sounds to the presence of the left-to-right shunt, and some to the presence of delayed electrical depolarization of the right ventricle.

THE development of safe and effective surgical techniques for the closure of atrial septal defects has increased the importance of accurate preoperative diagnosis. This lesion is common and, especially in younger patients, the physical signs may occasionally simulate those of a normal patient with a functional systolic murmur. Ancillary diagnostic methods that might obviate the need for cardiac catheterization would therefore be valuable. Atrial septal defect is characterized by a large left-to-right shunt with increased blood flow across the tricuspid and pulmonic valves and by delayed electrical depolarization of the right ventricle resulting usually in a pattern of incomplete right bundle-branch block in the electrocardiogram. Since both these features may produce distinctive changes in the heart sounds, phonocardiography may be an important technique in the correct diagnosis of this lesion. It is the purpose of this paper to describe the phonocardiographic features of 20 patients with uncomplicated atrial septal defect. Eleven of these patients were studied again after complete surgical closure of the defect. Since there was essentially no change in the electrocardiograms of these patients following surgery, this study has provided the unique opportunity of separate examination of the effects of the left-to-right shunt and of the delay of right ventricular depolarization upon the heart sounds in this lesion.

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MATERIAL AND METHODS

The diagnosis of atrial septal defect of the secundum variety was established in each patient by cardiac catheterization and further confirmed by surgical closure of the defect in 14 patients. Eleven of these patients had postoperative studies of their heart sounds. Complete closure of the defect in 10 of the patients was established by postoperative cardiac catheterization or by obvious complete surgical closure under direct vision with use of cardiopulmonary bypass.

The patients ranged in age from 4 to 50 years (mean 25 years). Left-to-right shunts were present in all patients and ranged from 2.1 to 22.4 L. per minute per M.² (mean 6.2 L. per minute per M.²). The systolic pressure in the pulmonary artery ranged from 16 to 65 mm. Hg (mean 34 mm. Hg). The duration of the QRS complex of the electrocardiograms ranged from 0.07 to 0.12 second (mean 0.09 second). Fifteen patients had incomplete right bundle-branch block and 1 had complete right bundle-branch block. Eighteen of 20 had secondary r waves or qR complexes in the right precordial leads, usually V₁.

Heart sounds were recorded with the patient in the relaxed recumbent position during quiet breathing or suspended respiration with a Sanborn Twin-Beam Cardiette at a paper speed of 75 mm. per second. A dynamic microphone supplied with the above apparatus was employed. Simultaneous electrocardiograms or carotid pulse tracings were recorded for timing purposes. In many patients, phonocardiograms were also recorded during cardiac catheterization, an electrocardiogram and intracardiac pressure being simultaneously recorded for timing. Reported time intervals consist of the mean value of measurements made from 10 successive cardiac cycles. The intensity of murmurs was graded from 0 to IV.

In all patients in this study measurements were made from the onset of the QRS complex of the electrocardiogram to the onset of pressure rise in the right ventricle and the pulmonary artery, as well as to the dicrotic notch of the pulmonary

artery pressure tracing. These intervals usually correlated well with the simultaneously recorded heart sounds but in all instances the sound provided a more precise point of reference than the event recorded on the pressure tracing. For example, it was usually difficult to determine the exact instant of the ascent of pressure in the right ventricle due to the initial gradual ascent of the pressure curve—whereas it was not difficult to identify precisely the onset of the sound of closure of the mitral and tricuspid valves. A study of heart sounds may therefore provide a more accurate method of examining the events of the cardiac cycle than examination of the pressure pulse.

Heart sounds were identified in the following manner: Pulmonic valve closure follows aortic valve closure and coincides with the dirotic notch of the pulmonary artery pressure tracing or with the crossover point of this tracing and the right ventricular pressure curve when there is no good dirotic notch. Aortic valve closure precedes the dirotic notch of the carotid artery tracing by approximately 0.01 to 0.03 second. This delay is due to pulse transmission from the left ventricle to the carotid artery, plus a very slight delay in the pulse recorder. Mitral valve closure precedes the onset of the carotid artery upstroke by approximately 0.04 to 0.06 second. This time interval is composed of the isometric contraction time of the left ventricle (about 0.04 second) and the pulse and instrumental delay described above. Tricuspid valve closure follows mitral valve closure and occurs simultaneously with the onset of pressure rise in the right ventricle. Systolic ejection sound of the pulmonary artery follows tricuspid closure and occurs simultaneously with the onset of pressure rise in the pulmonary artery.

Pressure events obtained by the cardiac catheter were corrected for the 0.01 second delay in transmission time through the catheter and recording apparatus.

Fifteen normal subjects with the same age distribution had phonocardiographic studies performed in a similar manner. All of these subjects had normal electrocardiograms and chest roentgenograms. None had any evidence of cardiac disease.

RESULTS

Splitting of the first heart sound was identified in all patients, the interval from mitral to tricuspid closure ranging from 0.02 to 0.05 second (mean 0.038 second). Splitting of the first sound was identified in all normal control subjects with a mitral-to-tricuspid closure interval ranging from 0.02 to 0.04 second

(mean 0.028 second). This range of normal values compares well with the previous work of Leatham.¹ An analysis of the individual measurements in both groups reveals a greater degree of splitting in the patients with atrial septal defect as suggested by the difference in mean values between the 2 groups (fig. 1). This difference in mean values is statistically significant at the 1 per cent confidence level according to Fisher's modification of Student's *t* test.² Following surgical closure of the defect there was essentially no change in the interval from mitral to tricuspid closure in the patients.

An early systolic ejection sound was recorded at the pulmonic area in 18 patients. A similar sound, but less intense, could be identified in the records of 7 of the control subjects. In occasional patients the ejection sound was loud and was responsible for an apparent wide splitting of the first sound on auscultation at the lower sternal margin. Following surgery the ejection sound diminished in intensity but did not disappear.

A systolic murmur was recorded at the pulmonic area in all patients. This murmur exhibited the following characteristics: 1. Its onset followed the first heart sound by a short interval of 0.04 to 0.08 second and the initial vibrations of the murmur were usually preceded by a systolic ejection sound. 2. It was an ejection murmur with its peak intensity in early or midsystole. 3. It ended before the sound of pulmonic valve closure and usually before the sound of aortic valve closure (fig. 2).

The murmur was of variable intensity and in some instances was faint or exhibited a scratchy character that suggested an innocent systolic murmur or a cardiorespiratory murmur upon auscultation. There was a rough direct correlation between the intensity of the murmur and the relative magnitude of the left-to-right shunt, the louder murmurs being associated with shunt volumes of 6 L. per minute per M.² or more. Two patients with grade-III murmurs had smaller shunts but these patients had prominent enlargement

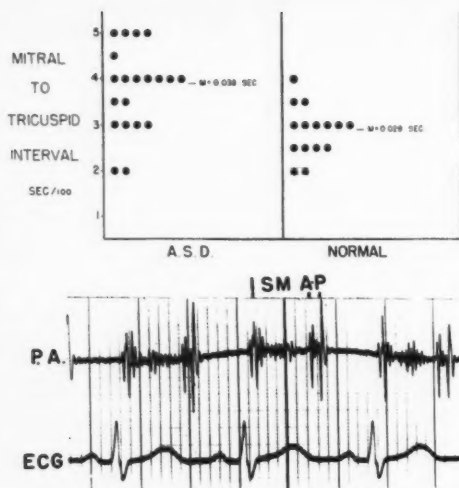


FIG. 1 Top. Each dot, mean value of 10 successive measurements of the interval from mitral to tricuspid valve closure in 1 subject. The difference between the mean values of the 2 groups is statistically significant.

FIG. 2 Bottom. The systolic ejection murmur of atrial septal defect recorded from the pulmonic area (P.A.) of a 7-year-old girl with a left-to-right shunt of 3.8 L./min./M.² 1, first heart sound; SM, systolic murmur; A, aortic valve closure; P, pulmonic valve closure. Subsequent illustrations will be similarly labeled. Time lines, 0.20 second.

of the main pulmonary artery demonstrated by chest roentgenograms. All patients with a loud murmur and a large shunt had a similar degree of pulmonary artery enlargement.

Following closure of the defect, the murmur disappeared in 3 patients and was greatly reduced in intensity in 8. It has been suggested by Cossio et al.³ that the systolic murmur in atrial septal defect is due to the increased blood flow across the pulmonic valve. If this concept is true, increasing pulmonary blood flow following closure of the defect should reproduce the murmur that was present prior to surgery. Pulmonary flow was increased by vigorous exercise in 8 patients and phonocardiograms were recorded immediately after exercise. In 6 of these patients, the original systolic murmur reappeared or the intensity of the residual systolic murmur increased (fig. 3). The characteristics of the

murmur induced by exercise were the same as those of the murmur present prior to surgery.

The second heart sound at the base is normally split, with pulmonic valve closure occurring 0.01 to 0.03 second after aortic valve closure in expiration. Inspiration increases this interval to values of from 0.03 to 0.0 second due largely to a prolongation of right ventricular systole¹ and probably also to shortening of left ventricular systole as demonstrated by Boyer and Chisholm.⁴ The interval from aortic closure to pulmonic closure during expiration in the 15 control subjects in this study ranged from 0.01 to 0.04 second (mean 0.028 second). The expected respiratory variation in this interval was noted in all of these subjects. In the patients this interval ranged from 0.04 to 0.09 second (mean 0.05 second) during expiration (fig. 4). On inspiration 12 of the 20 patients showed an increase of about 0.01 second in this interval. Following closure of the defect the interval from aortic to pulmonic valve closure returned to normal in 9 of the 11 patients studied. In 7 of these 9 patients the normal pattern of respiratory variation was also noted. In 1 patient, in whom complete closure of the defect had been demonstrated by postoperative cardiac catheterization, the interval remained unchanged at 0.06 second and showed no respiratory variation. One patient maintained a wide interval, but showed normal respiratory variation. The duration of the QRS complex of the electrocardiogram in these latter 2 patients was less than 0.10 second. At the time of the postoperative studies the heart rates were not exactly the same as in the preoperative studies but the difference in rates was small (mean 9 beats per minute) and this difference did not affect significantly the aortic to pulmonic valve closure interval.

An early diastolic murmur was present along the lower left sternal margin in 6 patients. This murmur began from 0.06 to 0.10 second after pulmonic valve closure and it was loudest at the time of early rapid diastolic filling of the right ventricle. At this time right ventricular diastolic pressure is lower than

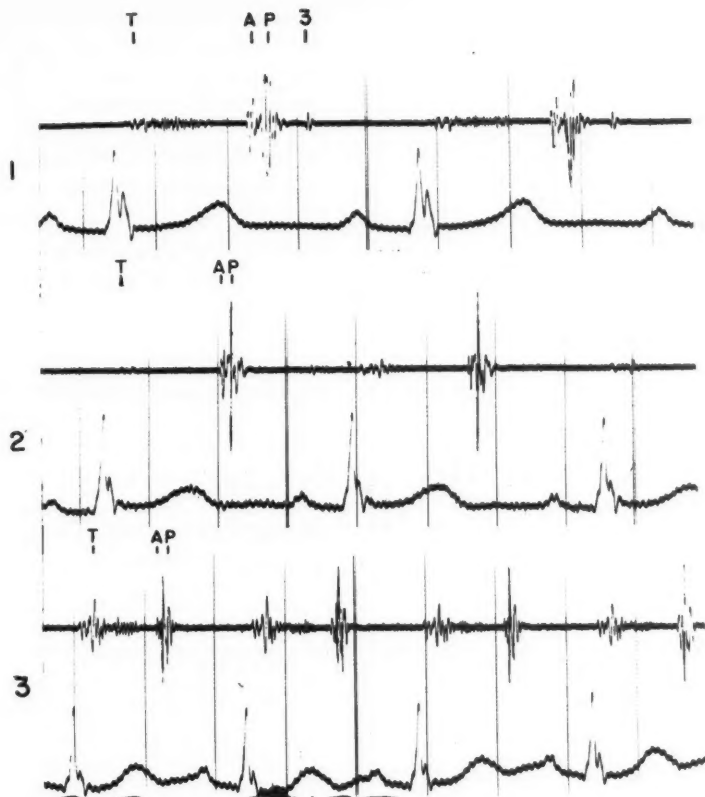


FIG. 3. *Line 1*, systolic murmur in a 20-year-old female with a left-to-right shunt of 7.9 L. per min. per M^2 . *Line 2*, same patient after closure of the defect showing disappearance of the murmur. *Line 3*, same patient after surgery and following exercise showing reappearance of murmur. Sounds recorded from the pulmonic area. *T*, tricuspid valve closure; *3*, right ventricular third heart sound.

later in diastole and a small pressure gradient can usually be demonstrated across the tricuspid valve. No relationship was noted between the size of the shunt and the presence of the murmur. The murmur disappeared following surgery in all cases.

Presystolic sounds were recorded at the cardiac apex in 8 patients. These sounds could not be detected by auscultation. These sounds were comparable to similar sounds recorded in normal subjects. No presystolic murmurs were observed. A faint apical third heart sound was recorded in 1 patient, which could not be identified by auscultation.

In 1 patient a sharp early diastolic sound was heard and recorded along the left sternal margin. It could not be recorded from the apex. It occurred 0.12 second after pulmonic valve closure and 0.06 second after the cross-over point of the right ventricular and right atrial pressures. It coincided with the trough of a slight early diastolic dip in the right ventricular pressure tracing (fig. 5).

DISCUSSION

Splitting of the first sound in atrial septal defect is not marked and cannot be differentiated by auscultation from physiologic split-

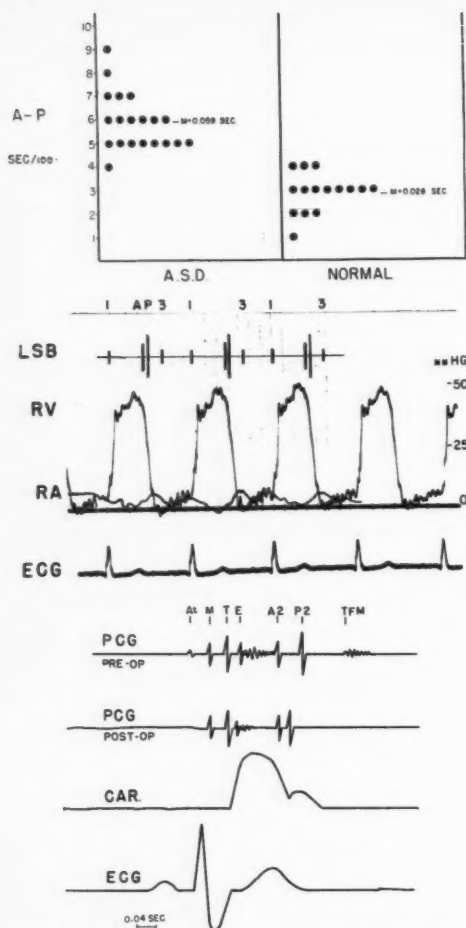


FIG. 4 *Top*. Each dot, mean of 10 measurements of the interval from aortic to pulmonic valve closure, measured in hundredths of a second, during the expiratory phase of respiration. The mean value for each group is recorded.

FIG. 5 *Middle*. Relationship of the heart sounds (LSB) to the pressure changes in the right ventricle (RV) and right atrium (RA). Pressure tracings were recorded during withdrawal of the catheter from the ventricle to the atrium, and then were superimposed. The heart sounds were recorded separately and then superimposed diagrammatically by selecting cycles of identical length. The pressures at the right of the illustration are referred to midchest. Time lines, 0.10 second.

FIG. 6 *Bottom*. Diagrammatic representation of the phonocardiographic features of atrial septal defect and the changes following closure of the defect. CAR, carotid artery tracing; A, atrial sound; M, mitral valve closure; E, systolic ejection click; TFM, tricuspid flow murmur.

ting of the first sound, except in the presence of complete bundle-branch block when the degree of splitting would be greater. The normal order of atrioventricular valve closure was present in all patients, with tricuspid valve closure following mitral valve closure. It might be expected that in atrial septal defect tricuspid valve closure would be delayed because the increased flow across the valve thrusts the leaflets deep into the ventricle throughout diastole. When ventricular systole occurs, more time is required for the leaflets to become tensed than if they had moved toward a position of partial closure just before ventricular systole. Cossio and Berkonsky⁵ have suggested that this mechanism results in a slight delay of the first heart sound in atrial fibrillation. Another explanation is that the delay in electrical depolarization of the right ventricle retards the onset of right ventricular systole and, thus, the sound of tricuspid closure. The fact that the degree of splitting of the first sound was not altered by complete closure of the defect suggests that delayed depolarization of the right ventricle is the factor responsible for the delay of tricuspid valve closure. Leatham and Gray⁶ noted wide splitting of the first sound in 6 patients with atrial septal defect who had complete right bundle-branch block and they were able to demonstrate the delay in right ventricular systole in 2 patients in whom catheterization of the right and left ventricles was performed. Comparison of the degree of splitting of the first heart sound in patients and in normal control subjects, as performed in this study, indicates that in atrial septal defect, even in the absence of complete right bundle-branch block, there is a slight delay in the onset of right ventricular systole producing an abnormal degree of splitting of the first sound. In studies of the time relationships of electrical to mechanical events of the cardiac cycle, Braunwald and associates⁷ found a delay in the onset of right ventricular systole in 11 of 21 patients with incomplete or complete right bundle-branch block patterns and a QRS duration of from 0.08 to 0.14 second. These findings were noted

patients with a variety of heart diseases, and, in another study,⁸ in 2 of 13 patients with no cardiovascular disease.

The systolic ejection sound produced by abrupt tension of the annulus of the pulmonary valve is a frequent finding in atrial septal defect because the transmission of the sound to the chest wall is facilitated by dilatation of the pulmonary artery.⁹ Since it may be present in normal subjects, its occurrence is of little diagnostic value unless it is loud or widely separated from the first heart sound.

The basal systolic murmur in atrial septal defect is undoubtedly produced at the pulmonary valve for the following reasons: 1. It is usually maximal at the pulmonic area. 2. It is an ejection murmur frequently initiated by an ejection sound. 3. Increased flow across the valve and dilatation of the pulmonary artery occur in atrial septal defects and could produce the murmur and facilitate its transmission to the chest wall. 4. At surgery a palpable thrill is present over the pulmonary artery, which disappears when the defect is closed. 5. Phonocatheter studies have demonstrated that the murmur is loudest at the pulmonic valve and faint or absent in the right ventricle or right atrium. The data in the present study suggest that 2 factors are involved in the production of the murmur: increased flow across the valve, and anatomic changes (dilatation) in the pulmonary artery. That the increased flow was not the only factor in the production of the murmur was suggested by the presence of residual systolic murmurs in 8 patients whose defects had been closed. Pulmonary blood flow was increased by exercise in 8 patients postoperatively and in 6 the systolic murmurs appeared or, if present, became louder. The phonocardiographic characteristics and the location of these murmurs induced by exercise were similar to those observed prior to surgery.

As other investigators¹⁰ have noted, respiratory variation in the degree of splitting of the second sound was present in many of the patients, although the magnitude of the variation was less than in the normal control subjects. That this is not apparent on auscul-

tation is due to the wide separation of the 2 components of the second sound in atrial septal defects, which makes small changes in the degree of splitting difficult to discern. The return of the degree of splitting to the normal range after closure of the defect indicates that the principal factor in the prolongation of right ventricular systole is the increased stroke volume and not the delay in depolarization of the right ventricle. Similar findings have been noted by others.^{10, 11}

Early diastolic murmurs at the lower sternal margin probably are due to increased flow across the tricuspid valve at the time of rapid right ventricular filling in early diastole. No increase in the loudness of the murmur was noted during inspiration as is frequently found in tricuspid stenosis or insufficiency. This is probably due to the fact that the large flow across the valve in atrial septal defect cannot be increased proportionately as much by inspiration as can the smaller flow across the valve in tricuspid disease.

A faint third heart sound recorded at the apex of 1 patient probably arose in the left ventricle and is similar to third heart sounds present in a great proportion of children and young adults.

An early diastolic sound audible along the left sternal border was recorded in 1 patient (figs. 3 and 5). It probably represents a third heart sound arising in the right ventricle for the following reasons: 1. The sound occurred too late to be produced by pulmonic valve closure or by an opening snap of the tricuspid valve. It occurred at the time of rapid right ventricular filling in early diastole. 2. The sound was loudest at the left sternal border over the right ventricle, while third heart sounds arising in the left ventricle are loudest at the apex and are only rarely loud along the left sternal border. 3. The sound occurred slightly later than a third heart sound arising in the left ventricle would be expected. Leatham and Gray⁶ recorded early diastolic sounds in 10 patients. In 8 of these the sound occurred 0.03 to 0.08 second after pulmonic valve closure, and it was suggested that this sound was an opening snap of the tricuspid

valve. In the 2 other cases, the sounds occurred 0.11 and 0.12 second after pulmonic valve closure and appeared to be similar to the sound discussed above. (In addition, we have recorded a sound with similar timing in 1 other patient with evidence of a left-to-right shunt at the atrial level demonstrated by a subsequent cardiac catheterization.)

The rare occurrence of third sounds in the right ventricle is pertinent to the general origin of the third heart sound. Surely the hemodynamic events accompanying left ventricular third sounds must occur as frequently in the right ventricle as in the left. The rapid filling of the right ventricle in atrial septal defect and tricuspid insufficiency, however, is rarely accompanied by third sounds. It is possible that the tricuspid valve and its chordae are thinner and more delicate and therefore less capable of producing a third sound when tensed than the thicker leaflets and chordae of the mitral valve.

While most of the above features of atrial septal defect can be elicited by careful auscultation, phonocardiography is of value in determining the degree of splitting of the first and second heart sounds, especially when one component is faint, as well as identifying the presence of systolic ejection sounds and the more rarely encountered early diastolic sounds. Following surgery auscultation will usually reveal the change in intensity or disappearance of the systolic murmur and the systolic ejection sound, the disappearance of the tricuspid flow murmur and the return to a normal degree of splitting of the second sound. Phonocardiography should make the latter determination more precise. Figure 6 represents the characteristic sounds and murmur and the postoperative changes diagrammatically.

SUMMARY

Phonocardiographic studies have been made of 20 patients with uncomplicated atrial septal defect and these studies have been repeated in 11 patients after complete surgical closure of the defect.

The following characteristic features were observed: Splitting of the first heart sound

due to the delayed onset of right ventricular contraction. Systolic ejection murmur at the pulmonic area initiated by a systolic ejection sound. Both are due to increased flow and dilatation of the pulmonary artery. Wide splitting of the second sound due to prolongation of right ventricular systole. Early diastolic murmur along the lower left sternal border probably due to increased flow across the tricuspid valve. Rare presence of a third heart sound arising in the right ventricle.

Following complete closure of the defect, the following observations were made: Persistence of the split first sound. Disappearance or decrease in the intensity of the systolic murmur and the systolic ejection sound. Decrease in the degree of splitting of the second sound. Disappearance of the tricuspid flow murmur and the right ventricular third heart sound.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Dr. Frank Gerbode who performed the cardiac surgery on the 14 patients described.

SUMARIO IN INTERLINGUA

Studios phonocardiographic esseva effectuate in 20 patientes con non-complicate defectos atrio-septal. In 11 patientes iste studios esseva repetite post le complete clausion chirurgie del defecto.

Le sequente observationes characteristic esseva facite: Fission del prime sono cardiac in consequentia del retardate declaration del contraction dextero-ventricular. Murmure de ejection systolic in le area pulmonic initiate per un sono de ejection systolic. Ambes es causate per augmentos del fluxo e del dilatation del arteria pulmonar. Fissura large del secunde sono in consequentia del prolongation del systole dextero-ventricular. Preeoce murmure diastolic al longo del margine sternal infero-sinistre, probabilemente in consequentia del augmento del fluxo a transverso la valvula tricuspid. In rar casos, le presentia de un tertie sono cardiac que prende su origine in le ventriculo dextere.

Post le complete clausion del defecto, le sequente observationes esseva facite: Persis-

entia del findite prime sono. Disparition o reduction del intensitate del murmure systolic del sono de ejection systolic. Reduction del grado de fission in le secunde sono. Disparition del murmure del fluxu triecuspide e del tertie sono dextero-ventricular.

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In the meantime this I know and declare to all men, that sometimes the blood passes in less, sometimes in more abundant quantitie, and the circuit of the blood is perform'd sometimes sooner, sometimes slower, according to the age, temperature, external and internal cause, accidents natural or innatural, sleep, rest, food, exercise, passions of the mind, and the like.—WILLIAM HARVEY. *De Motu Cordis*, 1628.

Renal Excretion of Sodium in Arterial Hypertension

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Patients with arterial hypertension excrete a sodium load more rapidly than do individuals with normal blood pressure. The relationship of this abnormal sodium excretory response to blood pressure and such extrarenal factors as the central nervous system, dietary salt intake, body fluid volume and sodium content, and the adrenal glands has been studied. On the basis of this and other evidence, it is suggested that the exaggerated natriuresis is the result of a renal tubular defect which occurs after the development of hypertension.

IT HAS been recognized since the studies of Farnsworth and Barker¹ that there is an abnormally high renal excretion of chloride in hypertensive individuals. Most subsequent research has been concerned with sodium rather than chloride. There have been several reports²⁻⁷ in which subjects with essential hypertension were observed to excrete an intravenous sodium load more rapidly than individuals with normal blood pressure. The explanation has been offered that this excretory derangement is related to alterations in renal function and that the high salt excretors were those hypertensive subjects whose renal plasma flow was reduced and filtration fraction elevated.⁸ Others,^{5, 6} however, have failed to observe such a relationship between increased sodium output and renal hemodynamics. The parallelism of the sodium clearance with both the level of the blood pressure^{2, 4-6, 9, 10} and renal vascular resistance⁶ suggested to Cottier et al.⁹ an alternative possibility, namely, that the hypertensive natriuretic response is related to the increased renal intravascular pressure. Baldwin and his associates,⁷ on the other hand, interpreted their results to indicate an extrarenal basis for the abnormal sodium excretion in essential hypertension.

The present study was undertaken to characterize further the hypertensive pattern of sodium excretion and the factors contributing to it. Consideration was given to the following: (1) the relationship of sodium excretion to blood pressure in subjects with labile, essential, and secondary hypertension; (2) the influence of extrarenal factors, such as the central nervous system, dietary salt intake, body fluid volume and sodium content, and the adrenal glands.

MATERIALS AND METHODS

The studies were performed on the following subjects: 16 with essential hypertension of varying severity, 4 with labile hypertension, 4 with secondary hypertension, and 11 with normal blood pressure. In the presentation of the data, the subjects with essential hypertension have been grouped in order of increasing blood pressure as follows: group I 130-160/90-110, group II 160-224/110-130, group III 236-240/134-140. Except for 2 patients with severe essential hypertension and diminished glomerular filtration there was no evidence of renal functional impairment. Cardiac decompensation was absent in all patients. The degree of retinopathy in the subjects with elevated blood pressure was grade II or less. There was no dietary restriction except when the effect of salt intake was being studied. No patient was receiving antihypertensive drugs.

Procedures, except when noted, were carried out at approximately the same time in the morning. Water and food were withheld from the preceding midnight until the completion of the study. The subjects were in the supine position. Whenever possible urines were collected through a soft rubber, multiholed, indwelling urethral catheter. In the remainder the specimens were voided and the

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collections checked for completeness by comparing the endogenous creatinine clearances for the several periods in each study. In the occasional instance when the correlation was poor the experiment was discarded. After a control urine collection of 60 to 90 minutes, 100 ml. 5 per cent sodium chloride per M^2 of body surface area (BSA) were administered intravenously over a 25-minute period. Urine specimens were then obtained 30, 60, 90, 120, and 180 minutes after the start of the infusion (for tabulation the last 2 periods have been averaged). Blood specimens were drawn during the control period and at the midpoint of all subsequent urine collections. When inulin and paraaminohippurate clearances were measured, 200 ml. water by mouth were given hourly beginning 2 hours before the start of the control period.

The possible influence of a center in the brain on renal sodium excretion was studied in 4 individuals with essential hypertension. Except for 1 patient (J.L.) all were hydrated with intravenous 5 per cent glucose in water at 3 to 4 ml. per minute. After a suitable baseline period, 5 per cent saline was infused into the right carotid artery at the rate of 1 ml. per minute for 25 minutes. This amount was calculated to increase the carotid serum sodium concentration 4 to 5 per cent without significantly altering that of the rest of the body.⁹ Urine samples were collected 60 minutes after the start of the infusion through an indwelling catheter.

Serum and urinary sodium and potassium were determined with an internal-standard flame photometer. Creatinine was measured by the method of Folin and Wu¹² as modified by Phillips.¹³ To assure complete recovery of creatinine proteins were precipitated at pH 2 by the procedure described by Owen et al.¹⁴ Inulin was determined by the Rolf, Surtshin, and White¹⁵ modification of the method of Alving, Rubin, and Miller¹⁶ and paraaminohippurate by that of Smith et al.¹⁷ Blood pressures were taken frequently throughout each study with a mercury sphygmomanometer.

RESULTS

Subjects with Essential Hypertension. Our results (table 1) show that subjects with essential hypertension excrete sodium more rapidly during the 3-hour period after the start of the hypertonic saline infusion than does a control group. A relationship can be noted between the rate of excretion and the

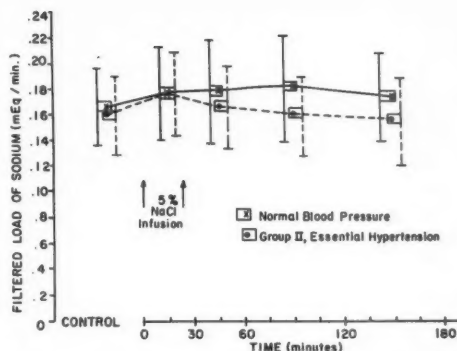


FIG. 1. The filtered load of sodium (ordinate) in subjects with normal blood pressure and group II essential hypertension is plotted against the time in minutes (abscissa). The vertical solid and dashed lines represent the standard deviation of the mean. Filtered load of sodium (mEq. per minute per $1.73 M^2$ BSA) = Endogenous creatinine clearance (ml. per minute per $1.73 M^2$ BSA) \times serum sodium (mEq. per ml.).

height of the blood pressure except in the 2 individuals comprising group III, who were known to have diminished glomerular function. Nevertheless, their sodium output was still increased over the normotensive levels.

The per cent of the infused sodium excreted during the first hour in 2 of the mild hypertensive subjects exceeded that observed in any of the controls while in the other 2 and all of the individuals with labile hypertension the values were within the normal range.

There is no evident difference in filtered sodium prior to or for the first hour following the salt load between the individuals with normal blood pressure and those in group II who showed the maximum excretion (fig. 1). During the second and third hours, however, the values for the control subjects are higher. Thus the sodium excretory response cannot be correlated with the filtered load.

Subjects with Secondary Hypertension. In table 2 the sodium excretory pattern following hypertonic salt loading in 2 patients with Cushing's syndrome and 2 with pheochromocytoma is comparable to that observed in the group II essential hypertensive subjects described in table 1. No correlation is noted between the natriuretic response and the

*It was assumed that the cerebral blood flow was 0.9 L. per minute¹¹ and that the right carotid artery received approximately a fourth of this amount.

TABLE 1.—Sodium Excretion in Individuals with Normal Blood Pressure, Labile and Essential Hypertension Following the Intravenous Infusion of 5 Per Cent Sodium Chloride*

	No. of subjects	Age	Control†	Sodium excretion (μ Eq./min.)			Per cent infused sodium excreted‡			Blood pressure (mm. Hg)
				I	II	III	I	II	III	
Normal blood pressure	11	Mean Range	98 (22-48)	180 (80-262)	189 (87-278)	229 (132-394)	1.6 (-0.2-3.2)	1.7 (-0.9-3.0)	10.1 (2.2-20.1)	113/71 (90-134) (60-86)
Labile hypertension	4	Mean Range	42 (18-42)	95 (42-124)	107 (64-155)	192 (148-231)	1.0 (0.3-1.7)	1.4 (0.6-2.6)	12.2 (8.1-16.7)	116/74 (105-130) (60-96)
Essential hypertension Group I	4	Mean Range	106 (26-44)	221 (151-308)	326 (242-497)	320 (230-428)	2.0 (1.2-3.1)	3.8 (2.9-5.5)	15.1 (10.8-17.5)	142/100 (130-160) (90-110)
Group II	10	Mean Range	138 (25-59)	676 (306-1475)	680 (421-1280)	406 (168-774)	10.8 (5.3-23.1)	11.0 (4.7-17.3)	20.9 (8.0-34.6)	184/116 (160-224) (110-130)
		<i>p</i> §	>.1	<.01	<.01	<.01	<.01	<.01	<.01	
Group III	2	Mean Range	58 (42-45)	297 (257-336)	276 (214-337)	269 (240-298)	4.3 (3.8-4.7)	3.9 (3.0-4.7)	13.2 (12.3-14.1)	238/137 (236-240) (134-140)

*The infused sodium load consisted of 100 ml. 5 per cent sodium chloride per M.² BSA.

†Control, 60-90 minutes prior to the start of the infusion; I, 0-30 minutes after the start of the infusion; II, 30-60 minutes after the start of the infusion; III, 60-180 minutes after the start of the infusion.

‡Per cent infused sodium excreted = $\frac{\text{mEq. sodium excreted in post-infusion period—}}{\text{period} \times \text{no. of minutes in post-infusion period}} \times 100$
 $\frac{\text{mEq. sodium excreted per minute during control}}{\text{mEq. sodium infused}}$

§The significance of the differences between the means for sodium excretion and per cent infused sodium excreted in the subjects with normal blood pressure and group II essential hypertension.

TABLE 2.—*Effect of Intravenous Infusion of 5 Per Cent Sodium Chloride* on Sodium Excretion in Individuals with Secondary Hypertension*

Patient, age, sex, diagnosis	5% Sodium chloride infused (ml.)	Period (min.)	Endogenous creatinine clearance (ml./min./ 1.73 M. ²)	Urine volume (ml./min.)	Sodium excretion (μ Eq./min.)	Per cent infused sodium excreted	Blood pressure (mm. Hg)	
							Systolic	Diastolic
D. L., 18, F, Cushing's syndrome	180	Control	98	1.35	219		220	150
		0- 30	102	2.40	610	7.6	200	140
		30-60	97	1.97	574	6.9	200	150
		60-180	105	1.50	412	15.1	200	142
W. K., 18, M, Cushing's syndrome	173	Control	111	1.78	366		130	90
		0- 30	123	3.96	920	11.3	148	103
		30-60	118	3.23	895	10.7	150	100
		60-180	111	2.17	610	19.9	135	95
L. J.,† 31, F, pheochro- moytoma	152	Control	103	1.19	191		195	120
		0- 30	117	2.48	452	6.3	200	120
J. E., 37, F, pheochro- moytoma	147	Control	114	0.62	122		200	120
		0- 30	114	1.32	370	5.9	180	108
		30- 60	120	1.81	386	6.2	170	110
		60-180	112	1.07	278	14.8	175	104

*The infused sodium load consisted of 100 ml. 5 per cent sodium chloride per M.² BSA.

†The study on L. J. had to be discontinued 30 minutes after the start of the infusion because of intensification of symptoms related to the pheochromocytoma. The symptoms were accompanied by a blood pressure of 230/160.

endogenous creatinine clearance. Fluctuations in urinary flow paralleled those for sodium excretion.

Effect of 5 per cent Sodium Chloride Infusions into the Carotid Artery. In 4 subjects with essential hypertension 5 per cent sodium chloride was infused into the right common carotid artery at a rate of 1 ml. per minute for 25 minutes. As previously explained, this procedure was designed to produce an increase in cerebral sodium concentration comparable to that achieved in this region by the intravenous administration of 100 ml. 5 per cent sodium chloride per M.² BSA, without, however, causing a significant elevation elsewhere in the body. As can be seen in table 3, no increase in sodium excretion similar to that following the usual intravenous hypertonic salt load was observed for the 60-minute period after the start of the infusion. The variation between the intravenous and carotid baseline sodium excretion in patients C.S. and S.T. may be explained by the fact that the studies were performed on different days on a free salt intake.

Except for J.L., the subjects were hydrated and their urinary flows were measured to determine whether the intracarotid hypertonic saline was being delivered to the cerebral osmoreceptors. In 1 of the hydrated subjects (W.C.) the apprehension and discomfort associated with carotid arterial puncture stimulated an antidiuretic response. However, in the 2 others (C.S. and S.T.) in whom satisfactory control urinary flows were obtained, the volumes fell during the infusion from 10.4 to 3.0 and 10.8 to 2.1 ml. per minute respectively, suggesting perfusion of the osmoreceptors.

Effect of Changes in Sodium Intake on Renal Response to an Intravenous Salt Load. As shown in table 4, a pronounced diminution in sodium excretion following the intravenous administration of 5 per cent saline is observed in 2 subjects with essential hypertension and 2 with Cushing's syndrome after 5 to 7 days of a 200 to 800 mg. sodium diet. This can be correlated neither with a fall in blood pressure, since in only 2 of the 4 subjects is a decrease noted, nor with a reduction in the filtered load of sodium.

TABLE 3.—*The Effect on Sodium Excretion of Infusing 5 Per Cent Sodium Chloride into the Carotid Artery*

Patient	Age	Sex	Blood pressure (mm. Hg)	Mode of administration	Sodium excretion† (mEq./hr.)		
					Total	Baseline	Total—Baseline
W. C.	39	M	194/112	Carotid Artery*	12.9	13.8	-1.1
				Intravenous†	23.9	13.0	10.9
J. L.	25	F	165/105	Carotid artery	8.3	10.3	-2.0
				Intravenous	29.9	11.0	18.9
C. S.	29	F	160/110	Carotid artery	24.1	14.4	9.7
				Intravenous	32.1	3.4	28.7
S. T.	40	F	170/110	Carotid artery	11.1	12.2	-1.1
				Intravenous	22.2	1.6	20.6

*The infusion of 5 per cent saline into the carotid artery was delivered at a rate of 1 ml. per minute for 25 minutes.

†The intravenous infusion consisted of 100 ml. 5 per cent sodium chloride per M.² BSA administered over a period of 25 minutes.

‡Total sodium excretion, mEq. sodium excreted during the 60-minute period following the start of the infusion of 5 per cent sodium chloride. Baseline sodium excretion, mEq. sodium excreted per minute during the control period preceding the infusion of 5 per cent sodium chloride multiplied by 60.

In a group I hypertensive patient, A.H., the extracellular fluid lost* during the period of sodium restriction was restored by the infusion of 1,500 ml. of isotonic saline over a period of 60 minutes. Immediately thereafter the sodium excretion following a salt load returned to that observed on a regular salt intake.

The effect of a high-sodium diet was studied in 1 normotensive individual. Increasing the intake of sodium from 4 to 8 Gm. per day did not alter the natriuretic response. However, on 12 Gm. per day the sodium excretion increased to borderline hypertensive levels. This was associated with a 5-pound gain in weight.

Effect of Acute Expansion of Body Fluid Volume on Sodium Excretion. To determine whether the abnormal natriuretic response observed in hypertensive patients following a 5 per cent saline load is the result of acute expansion of intravascular volume, 400 ml. of isosmotic albumin were administered to patient C.S. over a 25-minute period. This amount was estimated to expand the blood volume by an amount comparable to the 5 per cent saline. While sodium excretion rose (fig.

*Estimated on the basis of the fall in body weight.

2) the peak value occurred during the second hour after the infusion and was less than half of that achieved with hypertonic salt loading when the maximum response is noted during the first hour (fig. 3). The endogenous creatinine clearance increased slightly during the infusion and then remained above the baseline, as did the urinary sodium, for the remainder of the study. It is possible that the increase in sodium excretion may be explained by the increase in glomerular filtration rate, whereas this would not appear to be the case for the excretory response portrayed in figure 3. Urine volume rose during the infusion, but then fell progressively to the control level.

Expansion of extracellular fluid with isotonic saline containing the same amount of salt as the 5 per cent solution also failed to produce a comparable natriuresis (fig. 4).

There was no significant change in blood pressure during any of these studies.

DISCUSSION

Our results are consistent with those of others²⁻⁷ that individuals with essential hypertension excrete sodium more rapidly following a hypertonic salt load than do those with normal blood pressure. The degree of

response roughly parallels the elevation of the blood pressure (until there is impairment of renal function). In the labile hypertensive subjects and 2 of the 4 group-I hypertensive subjects, as contrasted with all of the group-II patients, the salt excretion pattern resembles the normal. This would suggest the possibility that the actual duration of the hypertension could also be an important factor. Furthermore, because the abnormal natriuretic response is observed after the development of the hypertension, this response should appear to be related to the hypertension per se and not to some inherent defect peculiar to the individual who is destined to become hypertensive.

The abnormal renal response to salt loading in secondary hypertension (Cushing's syndrome and pheochromocytoma) is further support for the primary role of high blood pressure, since, as is discussed later, hormonal imbalance does not appear to be etiologically related.

To determine how the hypertensive excretory response might be influenced by sodium intake, 2 subjects with essential hypertension and 2 with Cushing's syndrome were studied while on a low-sodium diet. In all instances sodium excretion following the salt load reverted to or toward normal. There are 3 likely explanations for the diminished response:

1. *Reduction in Filtered Load of Sodium.* Neither a decrease in serum sodium nor filtration rate was observed in our patients while on a restricted sodium intake. However, current methods are unable to discern small changes in glomerular function that could be significant in terms of sodium excretion.

2. *Increased Renal Tubular Reabsorption of Sodium.* This factor could reduce sodium excretion independently or in conjunction with a decrease in filtered load. It has been demonstrated in both man^{18, 19} and animals²⁰ that body sodium conservation during salt depletion is associated with increased tubular sodium reabsorption. This may occur in the absence of a significant fall in filtration rate.²¹ Our studies would support these observations since no relationship was noted between fil-

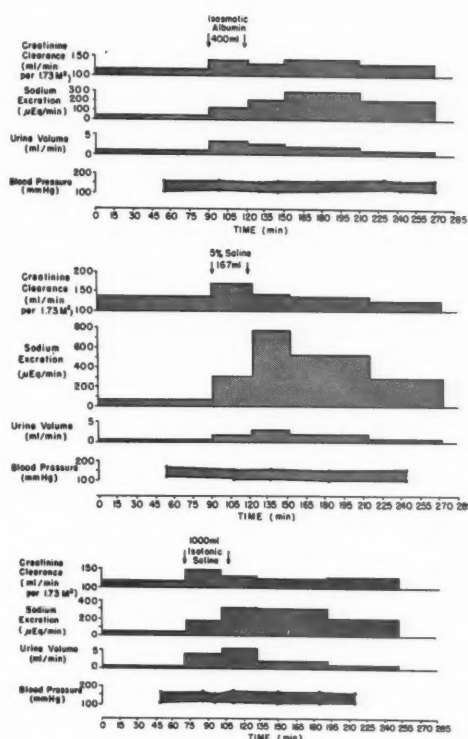


FIG. 2 *Top.* Sodium excretion in a subject (C.S.) with group II essential hypertension following acute expansion of intravascular volume with isotonic albumin.

FIG. 3 *Middle.* A representative study of the effect of the standard load of 5 per cent sodium chloride (100 ml. 5 per cent sodium chloride per M.² of BSA) on sodium excretion in a subject with group II essential hypertension. This is the same patient as represented in figure 2.

FIG. 4 *Bottom.* The effect on sodium excretion in patient C.S. of expansion of extracellular fluid volume with an isotonic saline solution containing approximately the same amount of salt as the 5 per cent sodium chloride solution referred to in figure 3.

tered and urinary sodium when salt intake was restricted. Furthermore, in patient A.H., the replacement with isotonic saline of the extracellular fluid lost during the period of sodium restriction restored the abnormal salt load response without a significant change in glomerular function. This finding is supported by the studies of Black et al.¹⁹ on the regulation of sodium excretion in normal and salt-depleted individuals. They observed that the

TABLE 4.—Effect of Changes in Sodium Intake on Sodium Excretion Following the Intravenous Infusion of 5 Per Cent Sodium Chloride*

Patient, age, sex, diagnosis	Sodium intake (Gm./day)	No. of days on diet	Weight (lbs.)	5% Sodium chloride infused (ml.)	Period (min.)	Endogenous creatinine clearance (ml./min./1.73 M ²)	Serum sodium (mEq./L.)	Filtered load sodium (mEq./min./1.73 M ²)	Urine volume (ml./min.)	Sodium excretion (mEq./min.)	Per cent infused sodium excreted	Inulin clearance (ml./min./1.73 M ²)	PAH clearance (ml./min./1.73 M ²)	Blood pressure (mm. Hg)	
														Systolic	Diastolic
Low sodium diet C.S., 29, F, essential hypertension	4.0		142	167	Control	134	147	19.7	0.56	57				150	104
					0-30	167			1.97	309	5.7			164	110
					30-60	140			3.30	764	14.8			154	100
					60-180	129			1.50	660	29.0			154	102
	0.2	5	140.5	167	Control	137	150	20.5	0.25	4				130	90
					0-30	171			0.47	24	0.4			150	100
					30-60	144			0.48	51	1.0			135	110
					60-180	139			0.61	51	3.9			150	100
					Control	89	140	12.5	1.06	160				130	90
					0-30	92			2.34	314	2.9			130	90
					30-60	99			1.60	380	4.1			138	90
					60-180	98			1.25	347	14.0			135	90
A.H., 26, F, essential hypertension	0.8	7	179.5	186	Control	86	141	12.1	0.24	3				132	90
					0-30	91			0.34	6	0.1			130	90
					30-60	97			0.33	15	0.2			130	90
					60-180	84			0.31	31	2.2			130	90
	0.8	13	178.8	1500ml. .9% saline	Control	100	141	14.1	0.43	28				130	90
					0-30	92			0.49	55				140	90
					30-60	111			4.48	169†				140	90
					60-90	97			3.67	285	2.1			140	90
					90-120	97			1.73	371	3.8			135	90
					120-240	107			1.63	392	16.8			145	100

*The infused sodium load consisted of 100 ml. 5 per cent sodium chloride per M² BSA.

†This value was used as the control sodium excretion in calculating the per cent infused sodium excreted.

TABLE 4.—Effect of Changes in Sodium Intake on Sodium Excretion, p. 11

Intravenous Infusion of 5 Per Cent Sodium Chloride* (Continued)

Patient, age, sex, diagnosis	Sodium intake (Gm./day)	No. of days on diet	Weight (lbs.)	5% Sodium chloride infused (ml.)	Period (min.)	Endogenous creatinine clearance (ml./min./1.73 M ²)	Serum sodium (mEq./L.)	Filtered load sodium (mEq./min./1.73 M ²)	Urine volume (ml./min.)	Sodium excretion (μEq./min.)	Per cent infused sodium excreted	Inulin clearance (ml./min./1.73 M ²)	PAH clearance (ml./min./1.73 M ²)	Blood pressure (mm. Hg) Systolic Diastolic
D.L., 18, F, Cushing's syndrome	4.0		168	180	Control	98	147	14.4	1.35	219				220 150
					0-30	101			2.40	610	7.6			200 140
					30-60	97			1.97	574	6.9			200 150
	0.2	6	165	180	60-180	104			1.50	412	15.1			200 142
					Control	82	142	11.6	0.55	35				170 130
					0-30	99			0.91	154	2.3			180 130
W.K., 18, M, Cushing's syndrome	4.0		155	173	Control	124	141	17.5	4.94	471		108	500	130 80
					0-30	132			6.68	840	7.5	132	621	130 80
					30-60	139			4.93	1040	12.2	137	641	140 90
	0.2	7	153	173	60-180	115			5.68	598	10.3	109	456	140 90
					Control	115	139	16.0	7.98	175		114	547	130 80
					0-30	107			4.24	357	3.7	112	475	130 80
High sodium diet C.R., 34, M, normal blood pressure	4.0		130	172	Control	145	142	20.5	0.45	93				110 80
					0-30	130			0.48	83	0.0			110 70
					30-60	141			0.53	109	0.3			110 70
	8.0	7	132.5	172	60-180	135			0.77	212	9.9			104 74
					Control	152	147	22.3	0.85	132				110 70
					0-30	128			0.94	203	1.4			110 80
12.0	12.0	6	135	172	30-60	142			0.87	180	1.0			110 80
					60-180	128			1.08	257	10.2			110 80
					Control	130	148	19.2	0.90	198				130 90
					0-30	148			1.84	383	3.8			120 80
					30-60	129			1.23	327	2.6			120 80
					60-180	141			1.75	534	27.3			130 80

*The infused sodium load consisted of 100 ml. 5 per cent sodium chloride per M² BSA.

increased sodium reabsorption noted while their subjects were on a rice diet persisted after the filtered sodium load was raised to normal levels, or higher, by the rapid infusion of saline. If, however, the period of infusion was lengthened from 20 minutes to an hour, as was the case in our patient, sodium reabsorption fell to within the normal range. They interpreted this delay in adjustment of renal function as indicating a hormonal mechanism and suggested that there may be an over-production of adrenal steroids. Corroborative evidence for this has been presented by Leaf and Couter¹⁸ and more recently by Bartter et al.,²² who, with methods of steroid analysis previously unavailable, demonstrated a correlation between aldosterone secretion and extracellular fluid volume. Thus the reduction in volume associated with the low-salt diet would act to enhance the tubular reabsorption of sodium by an increased production of mineralocorticoid. The opposite might occur with increased salt intake as shown by the borderline hypertensive response to intravenous 5 per cent saline observed in the normotensive individual (C.R.) on a sodium intake of 12 Gm. per day.

3. *Reduction in Blood Pressure.* Although the blood pressure fell in 1 patient with essential hypertension and 1 Cushing's patient during the period of sodium restriction, the absence of any change in the remaining subjects makes it unlikely that this contributed to the altered response.

As a possible explanation for the abnormal natriuretic response to a salt load in individuals with either essential or secondary hypertension, we postulated a cerebral sodium receptor exerting an effect on sodium comparable to that of the osmoreceptors on water. This could respond to alterations in cerebral sodium concentration and thereby control the renal tubular reabsorption of sodium. Such a center might become hyperactive in arterial hypertension, exerting a more pronounced effect on renal function. The literature contains reports of salt-losing syndromes associated with cerebral lesions.^{23, 24} In a patient carefully studied by Cort²⁴ interruption of

the hypothalamic tracts by a pleomorphic glioma produced excessive loss of sodium from the body. This could not be explained by renal disease or abnormal pituitary-adrenal function. We were unable, however, to demonstrate the existence of abnormally reactive cerebral sodium receptors. The infusion of hypertonic saline into the right common carotid artery, which is known to supply the pituitary gland and the major portion of the hypothalamus including the osmoreceptors, had no effect on sodium excretion. It still remains to be demonstrated, however, that the postulated sodium receptors do not exist in the areas supplied by the vertebral vessels. Technical difficulties related to percutaneous arterial puncture of these vessels have not permitted further evaluation of this aspect of the problem.

Also considered was the possibility that the hypertensive sodium excretion pattern could result from the expansion of body fluid volume by the 5 per cent saline through an increase in filtered sodium load. As can be seen in figure 1, however, the subjects with elevated blood pressure did not show values higher than the normal. Further evidence against a volume mechanism was our failure to elicit the typical abnormal natriuretic response in a hypertensive individual when isosmotic albumin or isotonic saline was administered. It is also unlikely that an acute increase in body sodium was a contributing factor, since the isotonic saline that contained an amount of salt equivalent to the 5 per cent sodium chloride solution failed to produce a comparable natriuresis.

The underlying mechanism responsible for the abnormal natriuretic response to salt loading in arterial hypertension is still a matter of debate. Since the filtered load of sodium is not increased, attention must be directed to other mechanisms influencing renal tubular transport. The participation of neurogenic factors (including neurohumoral) while deserving of consideration, is not suggested by the evidence. We were unable to demonstrate a cerebral sodium receptor that is sensitive to changes in serum sodium con-

centration. Furthermore, hypertensive subjects who have had thoracolumbar sympathectomy continue to show accelerated sodium excretion after receiving hypertonic saline.⁵ It has also been shown experimentally that renal denervation in unanesthetized dogs is not associated with alterations in renal function or electrolyte excretion.²⁵ On the other hand, it has been reported by Bricker et al.²⁶ that the sodium excretory response to changes in extracellular fluid volume differs from the normal in a completely denervated human kidney transplant. This data must be interpreted with caution, however, since it is possible that residual functional changes may have been produced by the 90-minute period of ischemia to which the kidney was subjected during surgery.

It is likewise difficult to attribute the abnormal renal electrolyte response to adrenal factors. In one of our patients with Cushing's syndrome (D.L.) who was studied after adrenalectomy while on a maintenance dose of cortisone (25 mg. per day), the natriuresis following a salt load remained above that of the control group.²⁷ Furthermore, sodium excretion never attained hypertensive levels when we administered cortisone to a normotensive individual.²⁷ Although Genest²⁸ has found increased urinary aldosterone excretion in patients with essential hypertension, there is as yet no conclusive evidence that aldosterone plays an important role in hypertension.²⁹ In both the Cushing's patient mentioned above and a hypertensive individual adrenalectomized for metastatic carcinoma of the breast whose blood pressure remained elevated postoperatively, the hypertensive excretory pattern was demonstrated in the absence of mineralocorticoid replacement therapy.²⁷

Concerning pituitary factors, Birchall et al.³ have observed that the antidiuretic response to an osmotic stimulus is normal in hypertension. Also, we were unable to reproduce the accelerated natriuresis of intravenous 5 per cent saline by subjecting the hypothalamic-hypophyseal system of hypertensive individuals to either expansion of

body fluid volume or cerebral hypernatremia comparable to that produced by the hypertonic salt solution.

Catecholamines, because of their effect on electrolyte excretion, must be considered in an evaluation of this problem. It has been shown by Smythe et al.³⁰ that the intravenous infusion of 1-norepinephrine, 1-epinephrine, and epinephrine promptly results in increased tubular reabsorption of sodium. Contrariwise, the chronic administration of epinephrine in oil is associated with increased sodium excretion.³¹ Since hypertension secondary to pheochromocytoma more closely resembles the latter situation, increased circulating medullary hormones could be a factor in the production of the accelerated natriuresis. This is unlikely, however, because the same load response pattern is observed in essential hypertension in which there is no conclusive evidence that these humoral agents are present in excess.³² Furthermore, in one of our patients with pheochromocytoma (J.E.), sodium excretion remained abnormal after removal of the tumor when urinary catecholamines had returned to normal levels.³³

There is evidence that hypertension is associated with metabolic alterations in renal tubular cells.^{34,35} Of particular interest are the histochemical studies of Shorr et al.³⁶ in which it was demonstrated that the distribution pattern in the kidney tubule of certain intracellular dehydrogenases is altered in both essential hypertension and the hypertension associated with Cushing's syndrome. The significance of these observations is enhanced by evidence suggesting that these enzymes may play a role in the renal transport of sodium.³⁷⁻³⁹ Further support for an intrinsic tubular lesion is the demonstration by Brodsky and Graubarth⁴⁰ that osmotic loading with mannitol produced a 2 to 2½ times greater sodium chloride excretion in hypertensive than normotensive individuals.

That the hypertensive subjects respond more normally to a salt load while on a low-salt diet in no way detracts from the concept of impaired tubular function, since Weston et al.⁴¹ have shown that the effect of mercurial

diuretics on sodium reabsorption can be counteracted by such sodium-conserving agents as DCA.

It appears reasonable, therefore, that the abnormal renal excretory pattern of sodium in arterial hypertension could result from a tubular metabolic lesion produced by a chronically elevated blood pressure.

SUMMARY

Subjects with essential hypertension and hypertension secondary to Cushing's syndrome and pheochromocytoma excrete sodium more rapidly following the intravenous administration of 5 per cent sodium chloride than do normotensive individuals. The abnormal sodium excretion pattern does not precede the development of hypertension. The degree of response to a salt load is roughly proportional to the elevation of blood pressure until there is impairment of renal function. It may also be related to the duration of the hypertension. Infusion of hypertonic saline directly into the carotid artery does not produce the abnormal renal excretion pattern in hypertensive subjects. Therefore, neither the hypothalamus, pituitary gland, nor other structures in the distribution of the carotid circulation respond to localized cerebral hypernatremia by altering the renal tubular transport of sodium. The accelerated natriuresis reverts toward normal in subjects with essential and secondary hypertension when dietary sodium is restricted. A borderline hypertensive response is observed in a normotensive individual while on a high-salt diet. The high sodium excretion in hypertension does not appear to be related to the effect of the intravenous saline on body fluid volume or sodium content. It is suggested that a renal tubular defect is responsible for the abnormal sodium excretory response to salt loading observed in hypertensive subjects.

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SUMMARIO IN INTERLINGUA

Le excretion de natrium post le administration intravenose de 5 pro cento de chloruro de natrium es accelerate in subjectos co hypertension essential o con hypertension secundari a syndrome de Cushing o pheochromocytoma in comparison con le responsa d subjectos normotensive. Le anormalitate de excretion de natrium non precede le desenvolvamento de hypertension. Le grado del responsa a un carga de sal es grossierment proportional al elevation del pression de sanguine usque il occurre un infraction del functional renal. Illo es etiam relationate possiblemente con le duration del hypertension. Le infusion de un hypertonic solution saline directemente in le arteria carotidie non evoca le mentionate anormalitate del excretion renal in subjectos con hypertension. Per consequente, ni le hypothalamo ni le corpore pituitari ni altere structuras in le distribution del circulation carotidie responde a localisate hypernatremia cerebral per effectuar un alteration del transporto de natrium in le tubulos renal. Le accelerate natriuresis redeveni normal in subjectos con hypertension essential o secundari quando le ingestion dietari de natrium es restringite. Un responsa limite de hypertension es observate in individuos normotensive quie ingere un dieta a alte contento de sal. Le alte excretion de natrium in patientes hypertensive non pare esser relationate con le effecto del sal intravenose super le volumine o le contento de natrium del liquidos corporee. Es presentate le these que un defecto reno-tubular es responsabile pro le anormalitate del responsa del excretion de natrium al cargation con sal que es observate in subjectos hypertensive.

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Autopsy Studies in Atherosclerosis

I. Distribution and Severity of Atherosclerosis in Patients Dying without Morphologic Evidence of Atherosclerotic Catastrophe

By JAMES C. ROBERTS, JR., M.D., CAMPBELL MOSES, M.D., AND
ROBERT H. WILKINS, B.S.

Gross lesions of atherosclerosis in many arterial sites were graded in 500 consecutive autopsies in a general hospital. The grading system used took into account both the total area of intimal involvement and the severity of individual lesions. The first report analyzes the distribution and severity of atherosclerosis in the 347 men and women of the study group who died *without* morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain. The second report describes the atherosclerotic lesions in patients who died *with* evidence of atherosclerotic catastrophe. The third report carries out a similar investigation in those subjects who presented evidence of obesity, hypertension, nephrosclerosis, and rheumatic heart disease.

THIS study was initiated to determine the distribution and severity of atherosclerosis in the major arteries of 500 consecutive adults dying in a general hospital. The present report describes the severity and distribution of atherosclerosis in the 347 patients from this group who died *without* morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain. The 2 succeeding papers deal with the atherosclerosis found in patients in the study group who died *with* evidence of atherosclerotic catastrophe,¹ and the distribution of atherosclerosis in patients with obesity, hypertension, nephrosclerosis, and rheumatic heart disease.²

METHODS AND PROCEDURES

The 3 hospitals from which the patients came are combined in 1 physical plant with common laboratory facilities. No obstetric patients are admitted to these hospitals and no pediatric patients came to autopsy. During the period of this study (September 1955 through August 1957) 16,962 patients were admitted, of whom approximately 47

per cent were male and 93 per cent were white. The hospital death rate was 4.4 per cent (732 patients), and 510 of these came to autopsy (70 per cent). Ten autopsies were excluded from the study because incomplete autopsy examinations were authorized. Brain examinations (75 per cent of the autopsied cases) were routinely performed unless specifically excluded by the family. Primary causes of death for the entire study group are listed in table 1. Distribution of the autopsied cases by age and sex are listed in tables 2 and 3. A total of 261 white men, 35 Negro men, 173 white women, and 31 Negro women (i.e., 59 per cent male patients, and 87 per cent white patients) were studied.

Thoracic and abdominal organs, including the arteries, were stored in Jores preservative; tissue blocks and the brain including cerebral arteries were fixed in 10 per cent formalin. After examination of tissue sections from the organs of each case, all final morphologic diagnoses were reviewed by one or more of 3 staff pathologists.*

When brain examinations were not performed, an average of 27 of 29 sites from 20 arteries were studied grossly and graded. When brains were examined, an average of 38 of 41 sites from 32 arteries was included. All arteries were opened longitudinally with the exception of occasional occluded, stenotic, or calcified small arteries. These were examined by transverse cross-sections every 2 to 3 mm. The cerebral arteries were dissected from the brain and at least 5-cm. segments of anterior, middle, and posterior cerebral arteries were

*Drs. T. J. Moran and R. S. Totten participated in this aspect of the study and gave important advice and assistance throughout.

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TABLE 1.—Primary Cause of Death

	Male	Female	Total
Cancer	131 (44%)	66 (32%)	197
Atherosclerosis	64 (22%)	20 (10%)	84
Renal disease	16 (5%)	20 (10%)	36
Gastrointestinal and liver diseases (other than above)	14 (5%)	21 (10%)	35
Rheumatic heart disease	18 (6%)	16 (8%)	34
Hypertension (other than above)	11 (4%)	9 (4%)	20
Diabetes mellitus	0 (0%)	15 (7%)	15
Syphilis and tuberculosis	10 (3%)	3 (1%)	13
Trauma	5 (2%)	5 (2%)	10
Other	27 (9%)	29 (15%)	56
Total	296 (100%)	204 (99%)	500

removed. The length of the vertebral artery segments varied, but they usually measured over 1 cm.

The grading system used combined both an estimate of area of total intimal involvement in a given site and the severity of the worst individual plaque at the site. Lipid stains were not used. If no atherosclerosis was observed (fig. 1A), the letter "O" was recorded. If less than 25 per cent of the area of the intimal surface was involved with any grossly visible lesions (fig. 1B), the degree of involvement was recorded as "A"; if 25 to 75 per cent of the intima was involved (fig. 1C), it was recorded as "B"; and if over 75 per cent was involved (fig. 1D), the site was recorded as "C."

The worst lesion at each site was then studied (no distinction was made between lipid and fibrous plaques). If the worst lesion was not ulcerated or thrombosed and its largest diameter was less than one fifth the inner circumference of the site (fig. 1E), a numerical value of 1 was added to the letter grade; if the plaque was larger than one fifth the inner circumference of the site, but without ulcer or thrombus, (fig. 1F), 2 was added to the letter grade; if an ulcer, but no thrombus, was present on any-sized lesion (fig. 1G), 3 was added to the letter grade; and if a thrombus (occlusive or nonocclusive) was present on any-sized lesion (fig. 1H), 4 was added to the letter grade. The grading was done by the authors in about one half the cases and in one half by residents who were instructed in the grading system.

For visualization of the atherosclerosis of the sites studied, "atherosclerosis profiles" were constructed by assigning to the letter grade O, A, B, or C the value 1, 2, 3, or 4, and adding this to the

number of plus signs recorded at each site. These 2 values were then averaged (table 4). The averages obtained were grouped for the various sex, race, and disease categories and charted as group atherosclerosis profiles.

Statistical analyses of the results observed in 8 areas were performed according to the Mann-Whitney U test,³ a nonparametric test. These were the right main coronary artery, the anterior descending coronary artery, the descending thoracic aorta, the middle of the abdominal aorta, the right internal iliac artery, the right renal artery, the right middle cerebral artery, and the basilar artery. A nonparametric test was necessary for analysis of our data because this type of statistical test does not make assumptions about the normal population distribution, and avoids the use of arithmetic processes on scores derived from a scale that does not have an absolute zero or equal units. Although in our grading system uninvolved areas were scored zero, the values assigned to involved areas were arbitrary and not necessarily separated by equal units.

In addition, the age, race, and disease distribution of patients was evaluated by means of the χ^2 , and Fisher exact probability tests, both of which compare the proportions of cases falling into various categories in one group with the proportions of cases falling into the same categories in another group. The χ^2 test was applied to those groups which contained more than 40 patients, and the Fisher test was employed when smaller groups were involved.³ The probability level of significance for all of these statistical tests was arbitrarily set at $p = 0.01$.⁹

Atherosclerotic catastrophes are defined in this study as recent or old myocardial infarcts; aneurysms of the aorta not due to cystic medial necrosis or syphilis; thrombotic occlusion of the abdominal aorta; and recent or old cerebral infarcts. The 347 patients who died without evidence of these catastrophes are the subjects of this report.

Figures 2 to 7 are the group atherosclerosis profiles of the various patients without atherosclerotic catastrophes; below each atherosclerosis profile are recorded the 8 sites that were studied statistically. The arteries are listed across the tops of the atherosclerosis profiles in the following order: right and left pulmonary; right and left main coronary; left circumflex coronary; anterior and posterior descending coronary; ascending, arch, and descending portions of the thoracic aorta; 3 segments of the abdominal aorta; 3 segments of right common iliac; 3 segments of left common iliac; right and

*Joseph F. Sunder, M.S., gave important advice and assistance in this phase of the study.

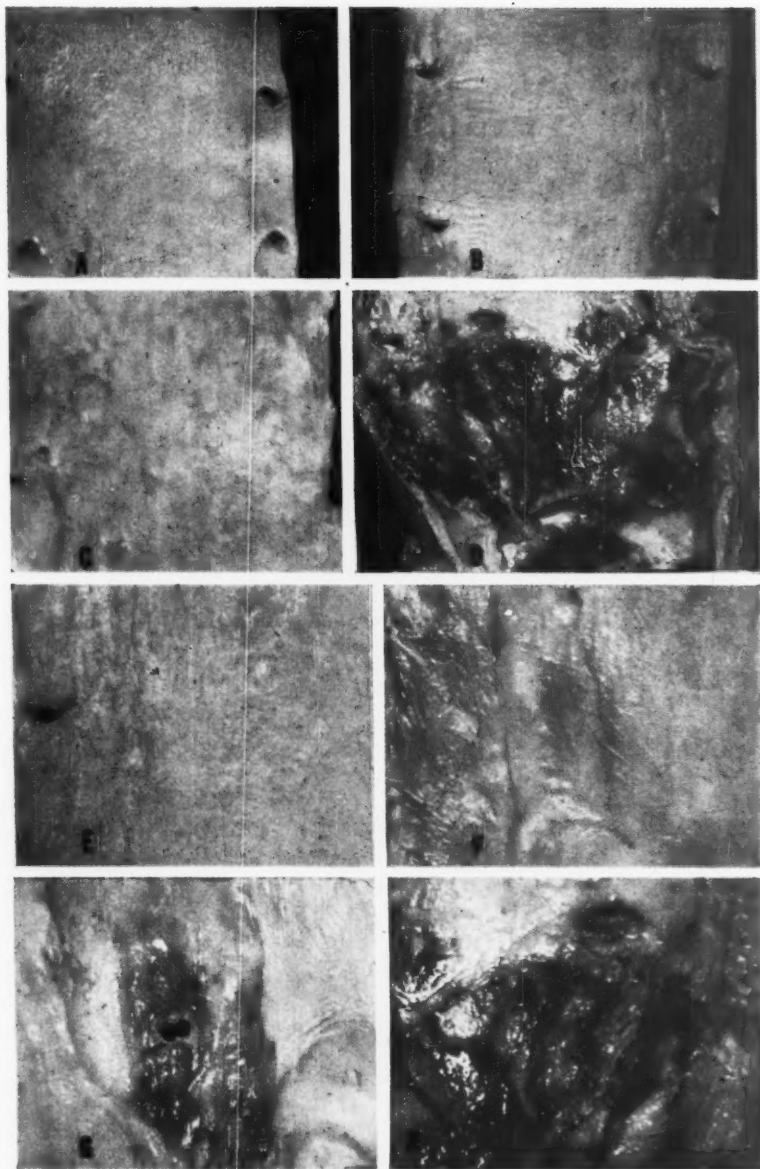


FIG. 1. *A*, area involved, grade 0; *B*, area involved, grade A; *C*, area involved, grade B; *D*, area involved, grade C; *E*, severity grade 1 plus; *F*, severity grade 2 plus; *G*, severity grade 3 plus; *H*, severity grade 4 plus.

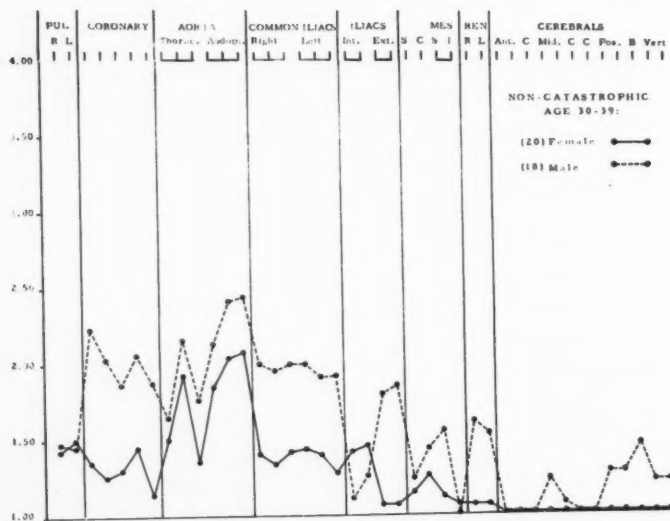
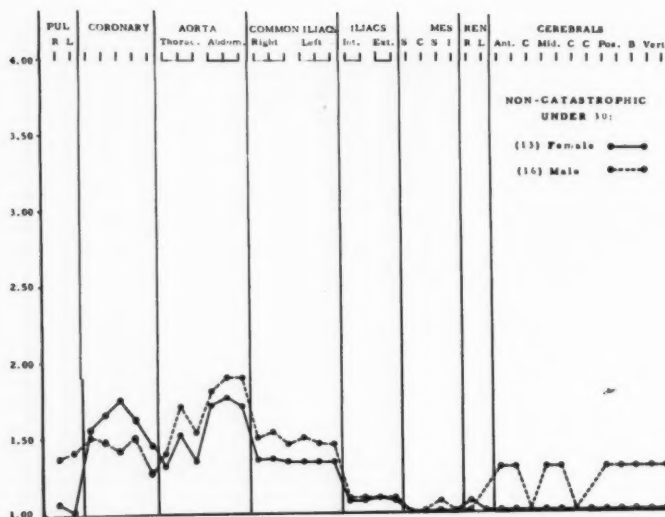


FIG. 2 Top. Ages 16-30. Statistical analyses. Right pulmonary, 0.160; right main coronary, 0.319; anterior descending coronary, 0.367; descending thoracic aorta, 0.087; middle abdominal aorta, 0.198; right internal iliac, 0.298; right renal, 0.460; right middle cerebral, 0.174; basilar, 0.174.

FIG. 3 Bottom. Ages 30-39. Statistical analyses. Right main coronary, 0.00003*; anterior descending coronary, 0.004*; descending thoracic aorta, 0.017; middle abdominal aorta, 0.040; right upper common iliac, 0.006*; right internal iliac, 0.097; right external iliac, 0.009*; right renal, 0.010*; right middle cerebral, 0.195; basilar, 0.053 (*Significant at 0.01 or less.)

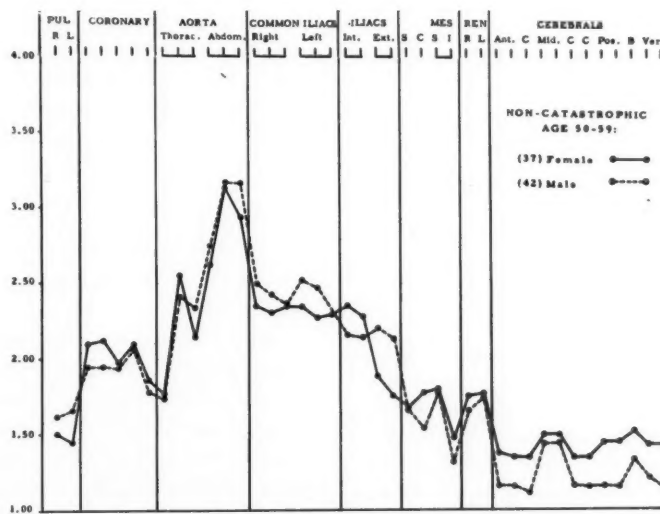
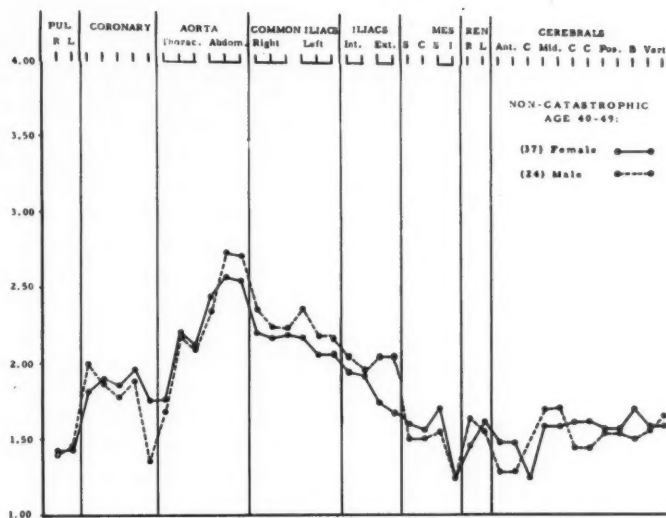


FIG. 4 Top. Ages 40-49. Statistical analyses. Right main coronary, 0.045; anterior descending coronary, 0.394; descending thoracic aorta, 0.323; middle abdominal aorta, 0.271; right internal iliac, 0.203; right renal, 0.230; right middle cerebral, 0.209; basilar, 0.206.

FIG. 5 Bottom. Ages 50-59. Statistical analyses. Right main coronary, 0.409; anterior descending coronary, 0.156; descending thoracic aorta, 0.037; middle abdominal aorta, 0.048; right internal iliac, 0.334; right renal, 0.145; right middle cerebral, 0.359; basilar, 0.365.

left internal iliac; right and left external iliac; splenic; celiac; superior and inferior mesenteric; right and left renal; right and left anterior cerebral; anterior communicating cerebral; right and left middle cerebral; right and left posterior communicating cerebral; right and left posterior cerebral; basilar; and right and left vertebral arteries.

RESULTS AND DISCUSSION

The distribution of atherosclerosis in the body at autopsy has long been the subject of morphologic studies.⁴⁻¹⁷ Most of these studies, however, have been either retrospective, selective as to patients, selective and incomplete as to the arteries studied, or based on grading systems which considered primarily either the worst area involved or the total intimal involvement. This study has been prospective and has included all patients autopsied in a general medical and surgical hospital. It has included as many cerebral, thoracic, and abdominal arteries as was feasible, and has been based on a grading system that takes into account both the area of most severe involvement and the total extent of intimal involvement.

The atherosclerosis profiles of these subjects dying without vascular catastrophes support the generally accepted views that atherosclerosis increases with age and involves primarily the larger arteries. Statistical analysis of these profiles demonstrates a significant sex difference in the distribution and severity of atherosclerosis only in the fourth decade and only in the coronary, iliac, and renal arteries. These data are in conflict with those of others who report prominent sex differences until the seventh decade.^{5-12, 18, 19} Although our data support the generally recognized view that males have more vascular catastrophes than females (table 2), the finding of similarly widespread and severe atherosclerosis in "non-catastrophic" males and females, suggests that the occurrence of catastrophes may be sex related, but that the extent and severity of atherosclerosis are not necessarily so influenced.

Pulmonary Arteries. The pulmonary arteries showed relatively few lesions of athero-

sclerosis at any age, no discernible differences between the sexes, and no differences between the right and left artery.

Coronary Arteries. In the men and women in this study, as in other reports,^{9, 10} the right main coronary artery and the anterior descending coronary artery generally contained the most severe coronary atherosclerosis.

In young men under 30 no artery had more than slight disease. Enos et al.¹³ found what they considered moderate to severe lesions in many men under 30 dying in Korea. However, their grading was based on the severity of single lesions rather than on both the extent and severity of involvement, and the subjects were healthy men, killed in action, rather than men with terminal disease.

Aorta. The abdominal aorta in all decades and in both sexes contained by far the most severe atherosclerosis, and the lower two thirds (below the orifice of the celiac artery) contained more than the first third. The arch of the aorta was the most severely involved portion of the thoracic aorta. The lack of atherosclerosis in the ascending aorta of our subjects was striking, and is at variance with older studies quoted by Allbutt.⁴ The explanation may lie in the decrease in syphilis over the years, since the few syphilitic cases we studied demonstrated severe lesions in the ascending aorta. Our data are in essential agreement with those of Gore¹⁵ and of Holman et al.¹⁶

Iliac Arteries. The common iliac arteries were similar to the arch and descending thoracic aorta throughout the decades and demonstrated sex differences only in the fourth decade. The internal iliac arteries had little atherosclerosis in either sex until the fifth decade, when significant disease in both sexes was readily demonstrable. The external iliac arteries of males of the fourth decade had an increased degree of atherosclerosis when compared with females, but no other sex difference was observed. Past the age of 50, the internal iliac arteries appeared to contain more atherosclerosis than did the external iliacs.

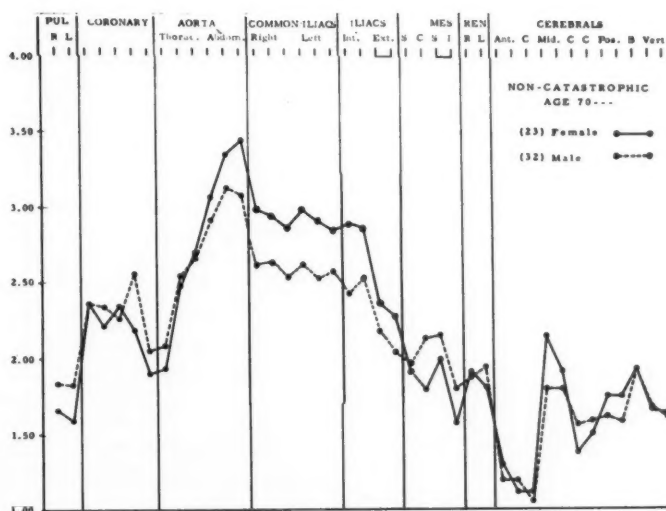
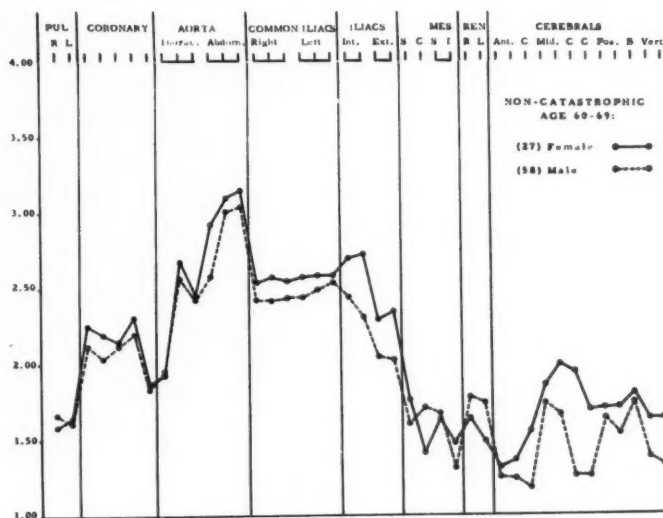


FIG. 6 *Top*. Ages 60-69. Statistical analyses. Right main coronary, 0.363; anterior descending coronary, 0.436; descending thoracic aorta, 0.484; middle abdominal aorta, 0.334; right internal iliac, 0.104; right renal, 0.014; right middle cerebral, 0.429; basilar, 0.268.

FIG. 7 *Bottom*. Ages 70-97. Statistical analyses. Right main coronary, 0.251; anterior descending coronary, 0.027; descending thoracic aorta, 0.245; middle abdominal aorta, 0.251; right internal iliac, 0.076; right renal, 0.417; right middle cerebral, 0.071; basilar, 0.444.

TABLE 2.—Age by Decades

Decade	Noncatastrophic		Catastrophic	
	Male	Female	Male	Female
16-30	16	13	0	1
30-39	20	18	2	0
40-49	24	37	9	4
50-59	42	37	26	12
60-69	58	27	30	15
70-97	32	23	37	17
Total	192	155	104*	49*

*The proportion of men with catastrophes is significantly larger than the proportion of women with catastrophes ($p = 0.01$).

TABLE 3.—Sex Distribution

	Male	Female	Total
Total studied	296	204	500
Noncatastrophic	192	155	347
Catastrophic*			
Heart	78	28	106
Brain	20	20	40
Aorta	26	10	36

*Several had multiple catastrophes.

TABLE 4.—Weighing the Extent and Severity of Atherosclerosis

Severity of worst lesion	Extent of intimal involvement			
	O	A	B	C
+	1.0	1.5	2.0	2.5
++	2.0	2.0	2.5	3.0
+++	3.0	2.5	3.0	3.5
++++	4.0	3.0	3.5	4.0

Splenic and Celiac Arteries. These vessels rarely had much atherosclerosis until the patients were beyond the age of 70, and no sex difference occurred. At any age they had less disease than almost any other vessels studied. This is again at variance with the older works quoted by Allbutt,⁴ wherein these vessels were listed high in the order of liability. These observers may have equated tortuosity and medial calcification with intimal lesions.

Mesenteric and Renal Arteries. The superior mesenteric artery and the renal arteries were similar to the splenic and celiac arteries at any age. There were no sex differences noted except in the renal arteries in

the fourth decade. The inferior mesenteric artery was almost uniformly without lesion—a finding also stressed by Allbutt.⁴

Cerebral Arteries. These arteries demonstrated no consistent pattern and were extremely variable. The thoracic and abdominal arteries tended to be moderately homogeneous in their distribution of lesions, but the cerebral arteries showed no such homogeneity and about 30 per cent (males 7/23; females 4/12) of the patients over 70 showed no gross atherosclerotic lesions in the 12 vessels examined. The anterior cerebral and communicating arteries had few lesions at any age and generally less than the other visceral and cerebral vessels. The posterior cerebral and vertebral arteries had somewhat more atherosclerosis than the anterior cerebral and communicating vessels. The middle cerebral and basilar arteries had the most atherosclerosis. Unfortunately, the internal carotid arteries were not included in the study. If a "parallelism" between the atherosclerosis of cerebral and visceral arteries exists,²⁰ it is not clearly evident in our material. In this series, cerebral atherosclerosis started later and remained less severe than that in visceral arteries of the same size. This is in agreement with the findings of Winter et al.¹⁷ but at variance with other reports.²⁰ The inclusion of cerebral examination in 75 per cent of the routine autopsies (without regard to antemortem cerebral findings) may explain the discrepancy of these data with reports²⁰ describing the presence of more and severe cerebral atherosclerosis in later years of life.

SUMMARY

The distribution and severity of gross atherosclerosis at autopsy in 347 patients dying without morphologic evidence of atherosclerotic catastrophes in the heart, aorta or brain have been graphically outlined. This study used a grading system for atherosclerosis that included consideration of both the extent and severity of intimal involvement. The observations included (a) the similarity of the severity and distribution of atherosclerosis in both sexes after the age of 40 (b) the lack of atherosclerosis in the cerebral

vessels of patients in the later decades, and (c) the minimal atherosclerosis in the pulmonary and abdominal visceral arteries.

ACKNOWLEDGMENT

The authors thank Mr. Allen Ellis for his loyal help in the study. The photography was performed by Mr. Albert Levin, F.B.P.A.

SUMMARY IN INTERLINGUA

Es delineate graphicamente le distribution e le severitate de atherosclerosis grossier notate in 347 necropsias de patientes morte *sin* evidencia morphologic de catastrophes atherosclerotic in corde, aorta, e cerebro. Le presente studio utiliza un systema de notas evaluatori pro le varie casos de atherosclerosis que prende in consideration tanto le extension como etiam le severitate del affection intimal. Le observationes include (a) le similitude del severitate e del distribution de atherosclerosis in le duo sexos post le etate de 40 annos, (b) le absentia de atherosclerosis in le vasos cerebral de patientes de etates plus avantiate, e (c) le presentia de atherosclerosis minimal in le arterias visceral pulmonar e abdominal.

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Autopsy Studies in Atherosclerosis

II. Distribution and Severity of Atherosclerosis in Patients Dying with Morphologic Evidence of Atherosclerotic Catastrophe

By JAMES C. ROBERTS, JR., M.D., ROBERT H. WILKINS, B.S., AND CAMPBELL MOSES, M.D.

THIS is the second of a series of reports on a study that was performed to observe the distribution and severity of atherosclerosis in the major arteries of 500 consecutive adults dying in a general hospital. The first report¹ dealt with atherosclerosis in the 347 patients from this group who died *without* morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain. The present paper describes the atherosclerosis in 153 patients in this group who died *with* morphologic evidence of atherosclerotic catastrophe. The third report² deals with the distribution and severity of atherosclerosis in patients from this study dying with obesity, hypertension, nephrosclerosis, and rheumatic heart disease.

METHODS AND PROCEDURES

Description of the subjects included in this study, and the methods employed in collecting and analyzing the data are detailed in the preceding paper.¹ Figures 1 to 9 are the group "atherosclerosis profiles" of the various patients with atherosclerotic catastrophes; below each atherosclerosis profile are recorded the sites which were studied statistically. The vessels are listed across the tops of the atherosclerosis profiles.

In the preceding paper, the "noncatastrophic" patients were subdivided into age groups and the distribution and severity of atherosclerosis in the various arteries discussed. Unfortunately, the catastrophic groups are of insufficient size for analysis by decades.

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RESULTS

Heart Catastrophes. Figures 1 to 3 summarize the atherosclerosis found in the males and females with evidence of myocardial infarction. When either of these groups was compared with age-matched controls (i.e., patients with no evidence of atherosclerotic catastrophe in the heart, brain, or aorta) it was obvious that those with catastrophes had significantly more atherosclerosis in almost all sites studied. When the females with catastrophes were compared with a randomly selected age-matched male group with catastrophes (fig. 3), the distribution and severity of atherosclerosis were almost exactly the same.

Cerebral Catastrophes. Figures 4 to 6 illustrate the atherosclerosis in the males and females with evidence of cerebral infarction. Unfortunately, the internal carotid arteries were not examined routinely in this study. When groups of either sex were compared with "noncatastrophic," age-matched controls, it appeared that those with cerebral catastrophes had somewhat more atherosclerosis in almost all sites (figs. 4 and 5). However, the differences were not so prominent as the differences noted in patients with cardiac or aortic catastrophes. Since both sex groups with cerebral catastrophes had almost the same age distribution, they were compared with each other, and the similarity of the groups with reference to atherosclerosis was striking (fig. 6).

Aortic Catastrophes. The profiles and statistical results from the males and females with evidence of aortic aneurysm or occlusive thrombosis are seen in figures 7 to 9. The males with these complications had much more atherosclerosis in all sites than their age-matched controls. In females this difference

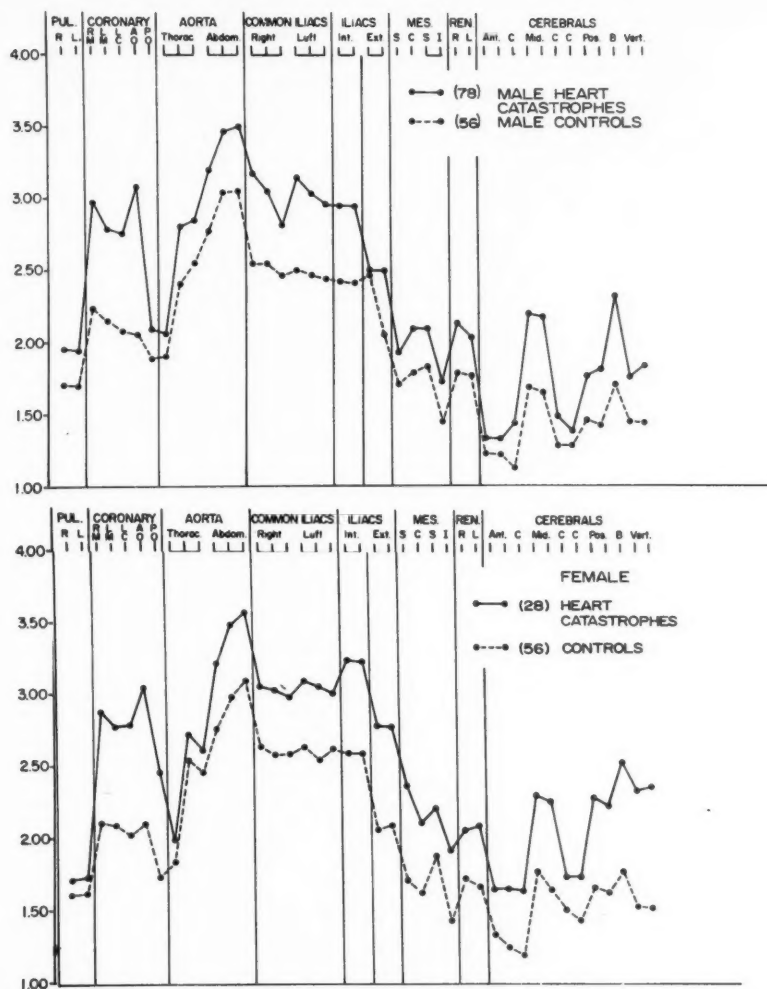


FIG. 1 Top. Heart catastrophes, males vs. controls. Statistical analyses (all significant at 0.01 or less): Right pulmonary, 0.001; right main coronary, 0.001; anterior descending coronary, 0.001; descending thoracic aorta, 0.001; middle abdominal aorta, 0.001; right internal iliac, 0.001; right renal, 0.001; right middle cerebral, 0.001; basilar, 0.001.

FIG. 2 Bottom. Heart catastrophes, females vs. controls. Statistical analyses. Right main coronary, 0.001*; anterior descending coronary, 0.001*; descending thoracic aorta, 0.028; middle abdominal aorta, 0.001*; right internal iliac, 0.001*; right renal, 0.003*; right middle cerebral, 0.007*; basilar, 0.001.* (*Significant at 0.01 or less.)

much less prominent. As in the cardiac and cerebral "catastrophic" groups, there were no significant differences in the atherosclerosis of the two sexes.

Multiple Catastrophes. Those patients with multiple catastrophes were too few for statistical evaluation.

CATASTROPHE CORRELATIONS

In patients of both sexes with cardiac catastrophes atherosclerosis in the abdominal aorta and cerebral vessels was significantly more severe than in control patients. In male patients with cerebral catastrophes the atherosclerosis in the abdominal aorta was also sig-

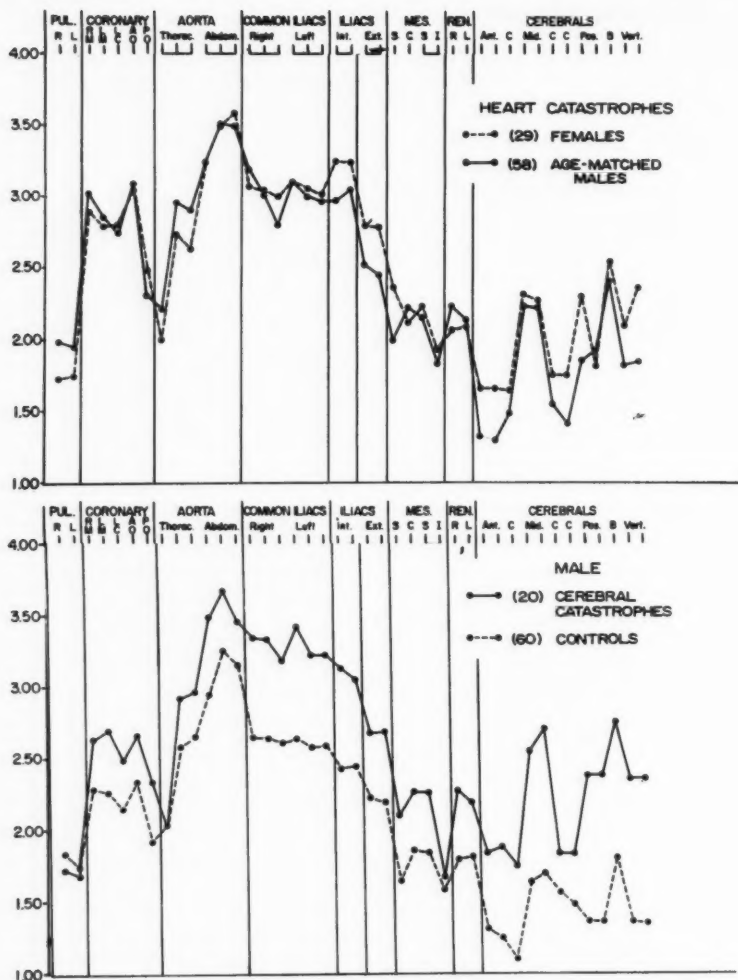


Fig. 3 Top. Heart catastrophes, males vs. females. Statistical analyses. Right main coronary, 0.189; anterior descending coronary, 0.413; descending thoracic aorta, 0.034; middle abdominal aorta, 0.480; Right internal iliac, 0.047; right renal, 0.255; left anterior cerebral, 0.010*; right middle cerebral, 0.039; basilar, 0.264. (*Significant at 0.01 or less.)

Fig. 4 Bottom. Cerebral catastrophes, males vs. controls. Statistical analyses. Right main coronary, 0.017; anterior descending coronary, 0.023; descending thoracic aorta, 0.044; middle abdominal aorta, 0.007*; right upper common iliac, 0.001*; right internal iliac, 0.002*; right renal, 0.033; right middle cerebral, 0.001*; basilar, 0.001*. (*Significant at 0.01 or less.)

nificantly more severe, but that in the coronary arteries was not. In female patients with cerebral catastrophes the findings were reversed (i.e., the atherosclerosis in the coronary arteries was significantly increased but that in the abdominal aorta was not). In patients with aortic catastrophes, again a sex

difference was noted: men with aortic catastrophes had diffusely more severe and widespread atherosclerosis than their controls, but women with aortic catastrophes had significantly increased atherosclerosis only in the abdominal aorta.

Pulmonary Arteries. As in the patient

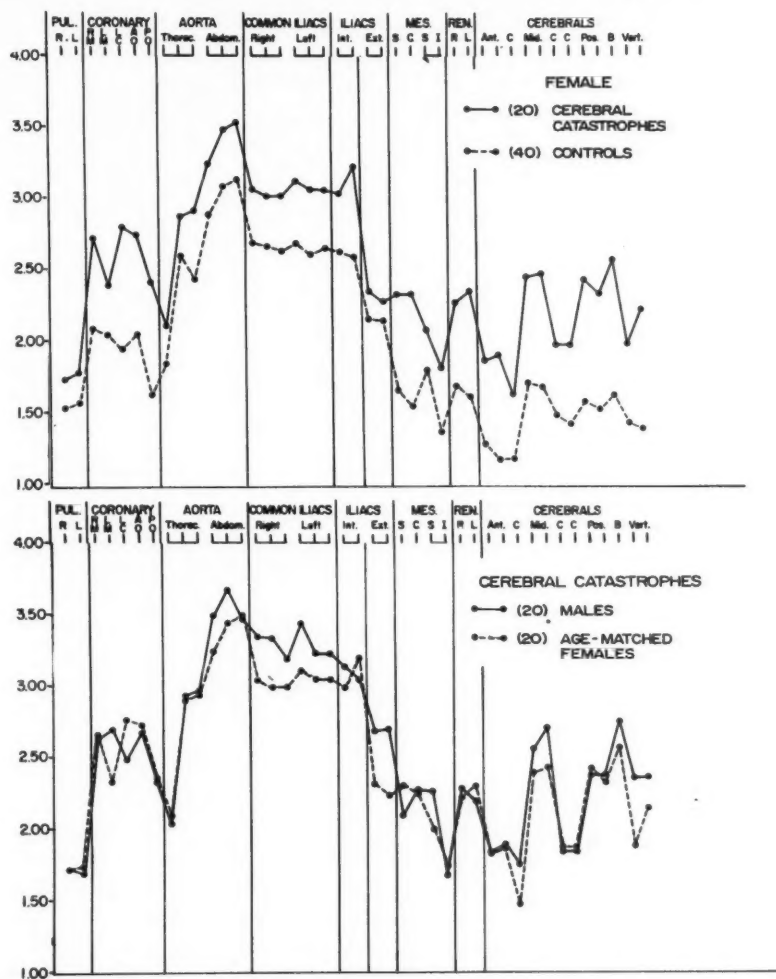


FIG. 5 Top. Cerebral catastrophes, females vs. controls. Statistical analyses. Right main coronary, 0.005*; anterior descending coronary, 0.004*; descending thoracic aorta, 0.009*; middle abdominal aorta, 0.018; right upper common iliac, 0.031; right internal iliac, 0.069; right renal, 0.003*; right middle cerebral, 0.006*; basilar, 0.001.* (*Significant at 0.01 or less.)

FIG. 6 Bottom. Cerebral catastrophes, males vs. females. Statistical analyses. Right main coronary, 0.464; anterior descending coronary, 0.421; descending thoracic aorta, 0.440; middle abdominal aorta, 0.264; right internal iliac, 0.305; right renal, 0.452; right middle cerebral, 0.312; basilar, 0.316.

without catastrophe,¹ the pulmonary arteries showed relatively little atherosclerosis. Significant increases were found only in males with cardiac catastrophes.

Coronary Arteries. In patients with catastrophes all coronary arteries showed more atherosclerosis than the coronary arteries of

the control patients. However, the posterior descending coronary arteries of the "catastrophic" patients were not so severely involved as the other major arteries. This difference among the arteries has been noted by others in "catastrophic" disease and by us in "noncatastrophic" disease.^{1, 3-5}

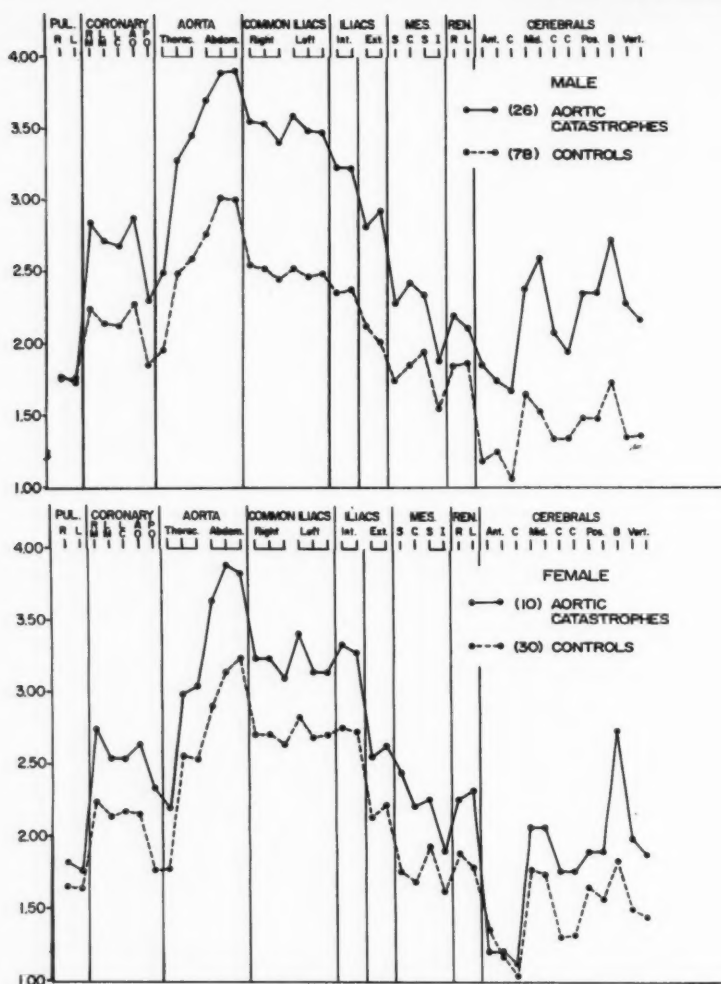


FIG. 7 Top. Aortic catastrophes, males vs. controls. Statistical analyses. Right main coronary, 0.001*; anterior descending coronary, 0.001*; descending thoracic aorta, 0.001*; middle abdominal aorta, 0.001*; right internal iliac, 0.001*; right renal, 0.022; right middle cerebral, 0.001*; basilar, 0.001.* (*Significant at 0.01 or less.)

FIG. 8 Bottom. Aortic catastrophes, females vs. controls. Statistical analyses. Right main coronary, 0.013; anterior descending coronary, 0.072; descending thoracic aorta, 0.097; middle abdominal aorta, 0.001*; right upper common iliac, 0.058; right internal iliac, 0.090; right renal, 0.078; right middle cerebral, 0.136; basilar, 0.022. (*Significant at 0.01 or less.)

Aorta. As in those patients studied with "noncatastrophic" atherosclerosis, the abdominal aorta contained more atherosclerosis than the other vessels. In patients with cardiac and cerebral catastrophes, however, this difference between aorta and other vessels was seldom as striking as in the "noncatastrophic" patients.

Iliac Arteries. The common iliac arteries demonstrated larger differences between the atherosclerosis of the study and control groups than did the abdominal aortas. In the previous report,¹ it was noted that the internal iliac arteries showed more atherosclerosis in the later decades than the external iliac arteries. This increased internal iliac athero-

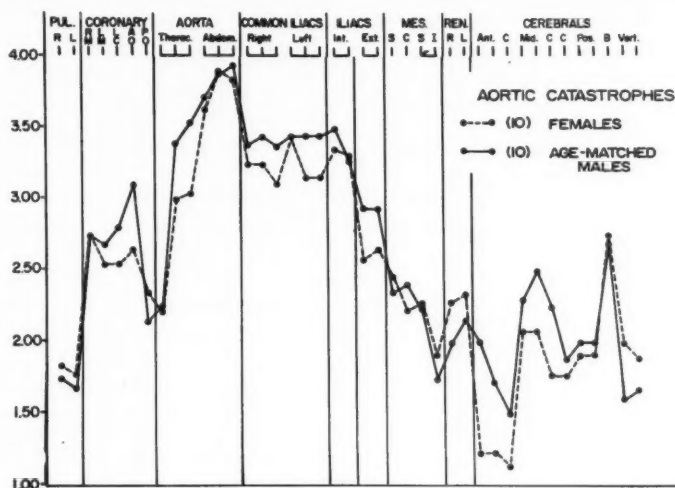


FIG. 9. Aortic catastrophes, males vs. females. Statistical analyses. Right main coronary, 0.348; anterior descending coronary, 0.164; descending thoracic aorta, 0.046; middle abdominal aorta, 0.456; right internal iliac, 0.047; right renal, 0.255; right anterior cerebral, 0.221; right middle cerebral, 0.227; basilar, 0.436.

sclerosis was even more evident among the "catastrophic" patients.

Splenic and Celiac Arteries. The atherosclerosis in these vessels was moderate, resembling that in the pulmonary arteries.

Mesenteric and Renal Arteries. The superior mesenteric artery and the renal arteries were similar to the splenic and celiac arteries, and rarely showed more than moderate atherosclerosis. The inferior artery rarely showed more than slight atherosclerosis.

Cerebral Arteries. As in the "noncatastrophic" patients these arteries demonstrated no consistent pattern and were extremely variable. Again, in common with the "noncatastrophic" patients, cerebral disease tended to be focal, whereas the thoracic and abdominal vessels were relatively homogeneous in severity and distribution. The anterior cerebral arteries and the anterior communicating artery rarely demonstrated more than light disease, and the basilar and middle cerebral arteries showed the most. The atherosclerosis in the posterior cerebral and posterior communicating arteries was intermediate between that in the above-mentioned vessels.

An observation emphasized in the preceding study¹ was the similarity in distribution and severity of atherosclerosis in "noncatastrophic" patients of both sexes after the age 40. The same similarity obtained in patients with catastrophes (figs. 3, 6 and 9). As indicated in the preceding paper,¹ table 2, a larger proportion of males had vascular catastrophes than did females. Thus, the occurrence of catastrophes may be sex related, but the extent and severity of atherosclerosis are not necessarily so influenced.

SUMMARY

The distribution and severity of gross atherosclerosis at autopsy in 153 patients dying with morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain were compared with that in 347 "noncatastrophic" patients. This study used a grading system for atherosclerosis that included consideration of both the extent and severity of intimal involvement. The study groups contained 78 males and 28 females with catastrophes in the heart, 26 males and 10 females with catastrophes in the aorta, and 20 males and 20 females with catastrophes in the brain. A significantly larger proportion of

men had vascular catastrophes than did women. However, there was no sex difference demonstrated in the distribution and severity of atherosclerosis.

SUMMARIO IN INTERLINGUA

Le distribution e le severitate de atherosclerosis grossier notate in 153 necropsias de patients morte *con* evidentia morphologic de catastrophes atherosclerotic in corde, aorta, o cerebro esseva comparate con le observationes correspondente in 347 casos "noncatastrophic." Le presente studio utiliza un sistema de notas evaluatori pro le varie casos de atherosclerosis que prende in consideration tanto le extension como etiam le severitate del affection intimal. Le serie includeva le casos de 78 masculos e 28 femininas con catastrophes cardiac, de 26 masculos e 10 femininas con catastrophes aortic, e de 20 masculos e 20 femininas con catastrophes cerebral. Un significativemente plus alte proportion de masculos que de femininas habeva catastrophes vascular. Tamen, nulle differentia sexual esseva demonstrabile in le distribution e le grado de severitate de atherosclerosis.

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Evans, W.: Hypertonia or Uneventful High Blood Pressure. *Lancet* 2: 53 (July 13), 1957.

The blood pressure was recorded in 400 consecutive healthy male military recruits. The behavior of the blood pressure was then observed in 200 of these individuals over a period of 10 years in 4 groups: 50 healthy recruits with normal blood pressure, 50 recruits with somewhat elevated blood pressure (180 mm. Hg systolic or 100 diastolic or both), 50 older male and female patients examined in private practice whose blood pressure was elevated without cardioarterial derangement (200 mm. Hg systolic or 110 diastolic or both), and 50 patients with proved arterial hypertension and cardioarterial changes. The normal recruits did not show any constant tendency toward an increase in blood pressure over the 10 year period. Forty-two of the 50 young adults with moderate hypertonia showed lower readings at the second examination compared to 10 years previously. Thus, moderately high values in young people did not presage a significant hypertension in later life. High blood pressure in older adults was not serious provided it was not associated with cardioarterial derangement manifested by refractory contraction of the lesser arteries and electrocardiographic evidence of left ventricular hypertrophy. The term hypertonia is proposed for the more benign state.

KURLAND

Autopsy Studies in Atherosclerosis

III. Distribution and Severity of Atherosclerosis in the Presence of Obesity, Hypertension, Nephrosclerosis, and Rheumatic Heart Disease

By ROBERT H. WILKINS, B.S., JAMES C. ROBERTS, JR., M.D.,
AND CAMPBELL MOSES, M.D.

THE preceding reports from this study have dealt with the atherosclerosis in patients dying with and without morphologic evidence of atherosclerotic catastrophe.^{1,2} In this report we present an analysis of the distribution and severity of atherosclerosis in the subjects of this study who presented evidence of obesity, hypertension, nephrosclerosis, or rheumatic heart disease.

METHODS AND PROCEDURES

With use of a grading system discussed previously,^{1,2} which takes into account both the total area of intimal involvement and the severity of individual gross lesions, up to 41 sites in 32 different arteries were graded in 500 consecutive autopsies at the Presbyterian, Eye and Ear, and Woman's Hospitals in Pittsburgh from October 1955 to September 1957. Description of the subjects included in this study and the methods employed in collecting and analyzing the data are partially discussed in the first paper of this series.¹ In table 1 is summarized the decade distribution of the various groups studied.

The weight and height of each patient were measured at autopsy and the weight-height index of Quetelet-Boucharde³ (i.e., weight in kilograms divided by height in centimeters) was calculated for each. With the assumption that a liter of serous fluid weighs approximately a kilogram, the weights of patients with measured ascites and pleural effusion were appropriately adjusted. After this adjustment the patients were arranged in serial order by their indices, and 4 standard deviations around the mean weight-height index were omitted. The remaining 47 heavy males and 30 heavy females

and their light counterparts were grouped for further study.

Translated into more familiar terms, the median indices of obese and thin patients can be expressed as the weight in pounds corresponding to any chosen height in inches. A height of 5 feet, 6 inches was found to correspond to 180 pounds in obese women and 98 pounds in thin women. Similar calculations for obese and thin men at a height of 5 feet, 10 inches were 191 pounds and 108 pounds, respectively.

Criteria for hypertension in this study were cardiac weights of over 500 Gm. for men and 400 Gm. for women, in the absence of significant valvular or pulmonary lesions which could have accounted for the cardiomegaly. Of the 47 obese men (40 white, 7 Negro) studied, 13 (28 per cent) were hypertensive (11 white, 2 Negro), and of the 30 obese women (24 white, 6 Negro), 13 (43 per cent) were hypertensive (9 white, 4 Negro). None of the 47 thin males (41 white, 6 Negro) and only 2 of the 30 thin females (25 white, 5 Negro) were hypertensive. In the entire autopsy series there were 38 men (32 white, 6 Negro) and 32 women (23 white, 9 Negro) with hypertensive cardiomegaly. Nonhypertensive patients (i.e., heart weights of less than 500 Gm. in males and 400 Gm. in females) are tabulated as normotensive in the present report.

The autopsy protocols were reviewed and the severity of benign nephrosclerosis, when it was present, was graded arbitrarily as 1, 2, and 3, on the basis of kidney weights and the degree of microscopic arteriolar hyalinization and necrosis. Among the 500 autopsied patients, there were 50 men (41 white, 9 Negro) and 42 women (32 white, 10 Negro) with nephrosclerosis of 2 or 3 severity.

There were, in addition, 22 men (21 white, 1 Negro) and 23 women (20 white, 3 Negro) who died because of rheumatic cardiac valvular involvement, of whom 8 men and 12 women had mitral stenosis.

Mainland⁴ pointed out that hospital populations, and especially autopsy populations, are not representative of the general population of sick persons, and that this can considerably bias the apparent relationships of diseases to one another. In our

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TABLE 1.—Age Distribution of Patients

	Men					Total males	Women					Total females
	Under 40	40-49	50-59	60-69	Over 70		Under 40	40-49	50-59	60-69	Over 70	
Caucasians	32	28	59	78	64	261	30	32	42	35	34	173
Negroes	6	5	9	10	5	35	12	9	7	7	6	31
Obese, hypertensive	1	3	6	3	0	13	0	4	3	5	1	13
Obese, normotensive	4	4	10	11	5	34	1	3	5	3	5	17
Thin, hypertensive	0	0	0	0	0	0	0	2	0	0	0	2
Thin, normotensive	8	0	11	17	11	47	5	5	5	5	8	28
Hypertensive	6	4	9	9	10	38	2	11	7	8	4	32
Normotensive	30	20	45	45	50	190	12	40	28	32	16	128
Nephrosclerosis	2	4	9	12	23	50	3	5	9	11	14	42
Age-matched controls	2	4	9	12	23	50	3	5	9	11	14	42
Rheumatic carditis	7	1	6	3	5	22	1	4	6	5	7	23
Age-matched controls	30	10	30	15	25	110	3	12	18	15	21	69

TABLE 2.— χ^2 and Fisher Tests

	Total number of patients	Total number of patients with catastrophes	p-value	Number of cerebral catastrophes	p-value	Number of aortic catastrophes	p-value	Number of cardiac catastrophes	p-value
Hypertensive men	38	27		5		4		24	
vs.			<0.001*		>0.200		>0.900		<0.001*
Nonhypertensive men	190	56		13		18		37	
Hypertensive women	32	17		10		1		10	
vs.			<0.001*		<0.001*		>0.500		<0.010*
Nonhypertensive women	128	21		9		4		12	
Obese, nonhypertensive men	34	15		0		4		12	
vs.			<0.010*		>0.020		>0.300		<0.010*
Thin, nonhypertensive men	47	6		4		2		3	
Obese, nonhypertensive women	17	6		2		2		4	
vs.			>0.050		>0.990		>0.500		>0.200
Thin, nonhypertensive women	28	3		2		1		2	

*Probability 0.01 or less.

study, community incidence and fatality rates of the diseases studied could not be determined, and so these areas remain undefined and possible sources of error. The race and sex distributions of the patients admitted to the hospital and of those autopsied were similar, however, and this adds support to the validity of our data.

Control groups, unless otherwise denoted, were selected in every instance from patients of the same sex from this same autopsy series. The controls were decade-matched, but otherwise randomly

selected (table 1). Atherosclerosis, obesity, and hypertension all become more severe with increasing age,^{1, 5, 6} but since the selection of control patients in this study involved decade-matching, distortion of results from unequal age distribution was minimized. In addition, in all of the study and control groups the patients were all of the same sex, thus eliminating bias due to difference in sex distributions. Although differences in atherosclerosis in white and Negro patients have been reported,^{7, 8} the racial distributions of the pa

TABLE 3.— χ^2 and Fisher Test

	Total patients	Patients with hypertension	p-value	Total nonhypertensive patients	Obese nonhypertensive patients	p-value
Men with aortic catastrophes	83	27	<0.001*	21	15	<0.010*
Control men	145	11		60	19	
Men with cerebral catastrophes	20	5	>0.010	4	0	>0.500
Control men	60	2		23	7	
Men with aortic catastrophes	26	4	>0.050	6	4	>0.100
Control men	78	2		31	10	
Men with cardiac catastrophes	78	24	<0.001*	15	12	<0.010*
Control men	156	5		54	20	
Total women with catastrophes	38	17	<0.010*	9	6	>0.100
Control women	122	15		36	11	
Women with cerebral catastrophes	20	10	>0.050	4	2	>0.200
Control women	40	3		9	1	
Women with aortic catastrophes	10	1	>0.700	3	2	>0.800
Control women	30	2		6	0	
Women with cardiac catastrophes	28	10	<0.010*	6	4	>0.090
Control women	56	5		13	3	

*Probability 0.01 or less.

patients in the several study and control groups in this series demonstrated no significant distribution differences by χ^2 and Fisher tests.

RESULTS

Incidence Relationships

As shown in table 2, male patients who died of or with atherosclerotic catastrophes had a significantly higher incidence of both hypertension and obesity than did men who had not experienced a vascular catastrophe. On the other hand, female patients with atherosclerotic catastrophes demonstrated only a

higher incidence of hypertension, when compared with female control patients. On further analysis, it was found that the incidence differences in men were significant only in those men who had experienced cardiac catastrophes, whereas there were no significant increases in the occurrence of hypertension or obesity in men with aortic or cerebral catastrophes. In contrast, women with either cardiac or cerebral catastrophes had a significantly greater incidence of hypertension than their controls.

Conversely, as demonstrated in table 3, both men and women with hypertension had a significantly greater number of atherosclerotic catastrophes, and especially of cardiac catastrophes, than did nonhypertensive patients. This was also true of obese, nonhypertensive men, but in contrast, the incidence of catastrophes was no higher among obese, nonhypertensive women than among their thin counterparts.

There was a significantly greater incidence of hypertension among obese patients of both sexes than among thin patients, and hypertensive patients were more often obese than were their normotensive colleagues.

Patients of either sex with nephrosclerosis were hypertensive more often than patients without this disease, and likewise, hypertensive patients had nephrosclerosis a significantly greater number of times than did normotensive patients.

Atherosclerosis Profiles

In the obese men studied, according to figure 1, the coronary arteries appear to be the only sites where atherosclerosis was more severe than in control patients. Furthermore, the presence of hypertension in these obese men demonstrates no additive effect on the degree of atherosclerosis in the various arteries. When the entire group of hypertensive men were examined with their control group (fig. 2), however, hypertension in males was found to be associated with an increase in the incidence and severity of atherosclerosis in both the coronary and cerebral arteries.

In women (fig. 3) obesity was not associ-

	Obese, hypertensive vs. thin	Obese, normotensive vs. thin	Obese vs. thin		Obese, hypertensive vs. thin	Obese, normotensive vs. thin	Obese vs. thin
Right main coronary	0.003*	0.002*	0.0003*	Right internal iliac	0.181	0.460	0.309
Anterior descending coronary	0.005*	0.002*	0.0003*	Right renal	0.326	0.031	0.093
Descending thoracic aorta	0.334	0.386	0.484	Right middle cerebral	0.036	0.195	0.386
Middle abdominal aorta	0.288	0.040	0.037	Basilar	0.500	0.429	0.496

* Significance at 0.01 or less.

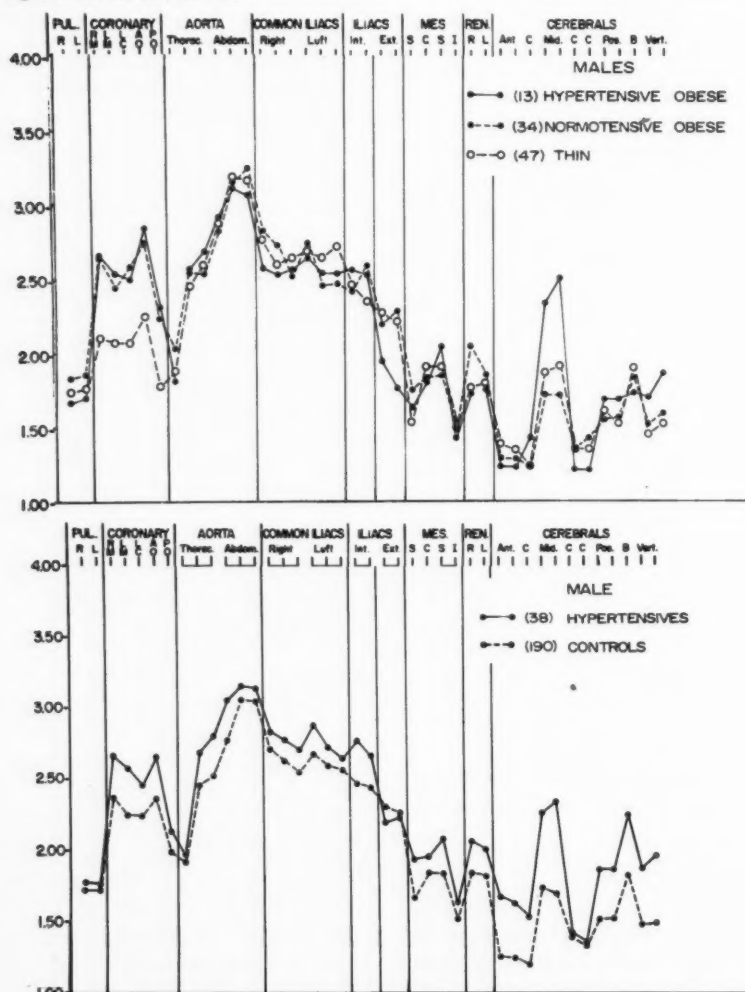


Fig. 1 Top. Mann-Whitney U Test: Probability (p) Values.

Fig. 2 Bottom. Mann-Whitney U Test: Probability (p) Values. Statistical analyses. Right main coronary, 0.002*; anterior descending coronary, 0.010*; descending thoracic aorta, 0.016; middle abdominal aorta, 0.460; right internal iliac, 0.027; right renal, 0.052; right middle cerebral, 0.00005*; basilar, 0.003.* (*Significance at 0.01 or less.)

ted with increased atherosclerosis in any of the arteries studied, but hypertension, on the other hand, was associated with a striking increase in several areas. When all of the females with hypertension were studied (fig. 1), this increase was found to be even more marked and to include almost all of the vessels studied.

Although no illustrative figures are included in this report, there was no difference noted between the atherosclerosis of thin men and thin women. Likewise, the atherosclerosis profiles of obese, normotensive males and females, and of all the obese males and females resembled each other. Obese, hypertensive females, however, had more severe and widespread atherosclerosis than their male counterparts in their iliac and cerebral arteries. On the other hand, no quantitative differences were noted between the atherosclerosis of the entire group of hypertensive men and age-matched hypertensive women.

The amount of atherosclerosis in patients with nephrosclerosis, with few exceptions, resembled that occurring in patients with hypertension.

Although the pulmonary arteries in the men and women with rheumatic carditis appeared on the profiles to contain more widespread and more severe atherosclerosis than the pulmonary arteries of control patients, this was not statistically significant (figs. 5 and 6). There were no significant differences in any of the other arteries studied in these 4 groups. Men and women with mitral stenosis also appeared to have more severe and widespread atherosclerosis in their pulmonary arteries than did their controls, but these groups did not contain enough patients for adequate analysis. No quantitative differences were noted between the atherosclerosis of men and age-matched women with rheumatic heart disease.

DISCUSSION

Obesity and Atherosclerosis

Most observers have failed to find a direct relationship between atherosclerosis and obesity.⁹⁻¹¹ There does seem to be a correlation, however, with physique, and atherosclerosis

in men is thought to be earliest in onset and most severe in those with mesomorphic build.^{12, 13} Wilens^{5, 14} has pointed out that, since any change in nutrition that occurs with fatal disease is usually in one direction (i.e., well nourished to poorly nourished), any terminal thin group will include some persons who were formerly normal or obese. Therefore, he concluded that terminal loss of weight would tend to reduce rather than to exaggerate any true differences in the amount of atherosclerosis, if these were present, between obese and thin patients.

Various studies have shown that there is an increased incidence of both hypertension and diabetes in obese people,¹⁵⁻¹⁷ and patients with either hypertension or diabetes are more prone than patients without these diseases to develop severe atherosclerosis and to experience atherosclerotic catastrophes.¹⁶⁻²⁰ Unfortunately, the number of patients with diabetes in this study was too small for statistical evaluation, but the presence of obesity in our nonhypertensive patients was not associated with an obviously increased incidence of diabetes. There was, however, a significantly greater occurrence of hypertension among obese patients of both sexes.

In our patients, obesity that was uncomplicated by hypertension appeared to influence significantly the severity and distribution of atherosclerosis only in the coronary arteries, and only in men. In obese, nonhypertensive men, compared with thin, nonhypertensive men, there was not only more widespread and severe coronary atherosclerosis, but also a greater number of cardiac atherosclerotic catastrophes.

Hypertension and Atherosclerosis

Agreeing with Goldenberg et al.,²¹ that autopsy heart weight is the most reliable pathologic criterion of hypertension, in this study we used a weight of 400 Gm. for female hearts and 500 Gm. for male hearts as the top normal weights. These normal standards were set at slightly heavier weights than those used by previous authors,^{22, 23} since it was considered that this would give sharper differentiation between hypertensive and normo-

	Obese, hypertensive vs. thin	Obese, normotensive vs. thin	Obese vs. thin		Obese, hypertensive vs. thin	Obese, normotensive vs. thin	Obese vs. thin
Right main coronary	0.012	0.302	0.057	Right upper common iliac	0.001*	—	—
Anterior descending coronary	0.011	0.152	0.022	Right internal iliac	0.097	0.251	0.063
Descending thoracic aorta	0.345	0.305	0.326	Right renal	0.099	0.397	0.189
Middle abdominal aorta	0.008*	0.134	0.019	Right middle cerebral	0.001*	0.433	0.042
				Basilar	0.001*	0.413	0.050

*Significance at 0.01 or less.

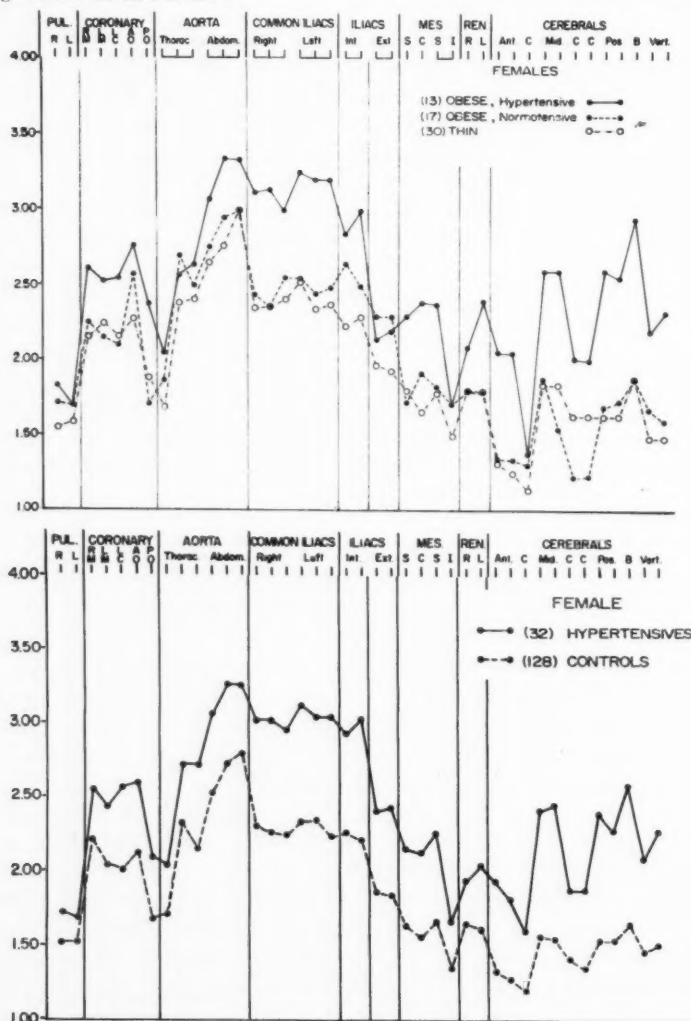


FIG. 3 Top. Mann-Whitney U Test: Probability (p) Values.

FIG. 4 Bottom. Mann-Whitney U Test: Probability (p) Values. Right main coronary, 0.00003*; anterior descending coronary, 0.0003*; descending thoracic aorta, 0.0003*; middle abdominal aorta, 0.0005*; right internal iliac, 0.00003*; right renal, 0.0005*; right middle cerebral, 0.00003*; basilar, 0.00003.* (*Significance at 0.01 or less.

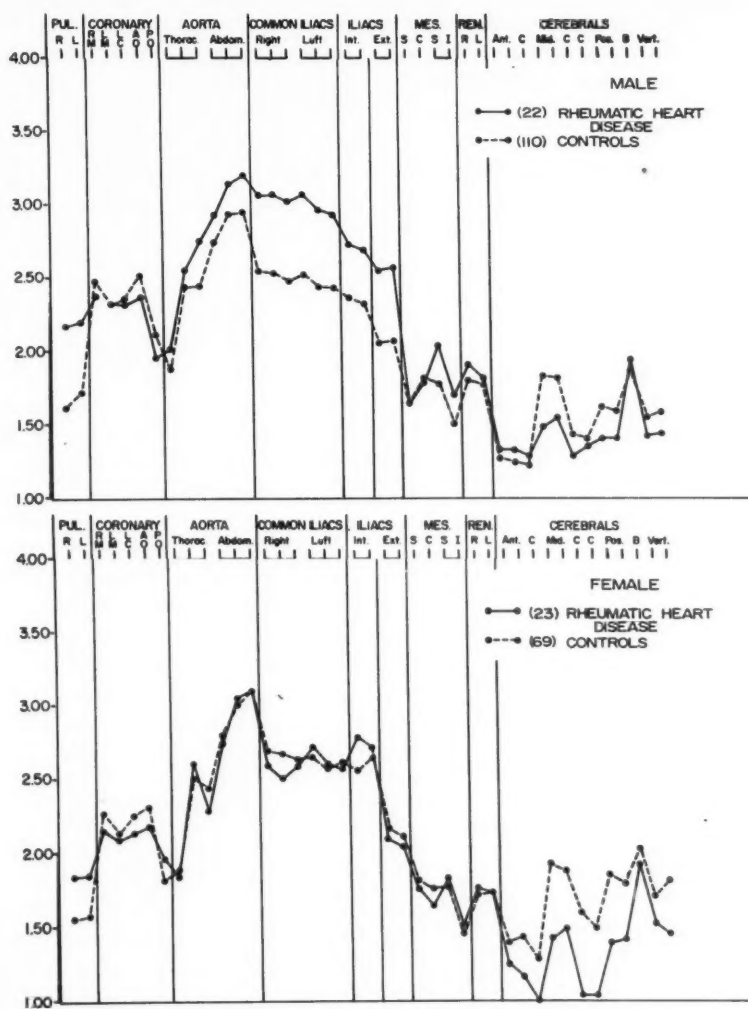


FIG. 5 Top. Mann-Whitney U Test: Probability (p) Values. Statistical analyses. Right pulmonary, 0.012; right main coronary, 0.248; anterior descending coronary, 0.164; descending thoracic aorta, 0.082; middle abdominal aorta, 0.169; right internal iliac, 0.140; right renal, 0.500; right middle cerebral, 0.026; basilar, 0.464.

FIG. 6 Bottom. Mann-Whitney U Test: Probability (p) Values. Statistical analyses. Right pulmonary, 0.011; right main coronary, 0.187; anterior descending coronary, 0.261; descending thoracic aorta, 0.278; middle abdominal aorta, 0.184; right internal iliac, 0.255; right renal, 0.117; right middle cerebral, 0.035; basilar, 0.298.

ensive patients, especially in light of the reported ability of uncomplicated coronary artery disease to cause cardiac hypertrophy.²⁴

Obesity is reported to be more common among hypertensive than normotensive pa-

tients,^{10, 16} and this was the case with our patients. Since obesity in our study group, however, was found in general to exert only a minor influence on the degree of atherosclerosis, our hypertensive patients were not cate-

gorized as to the presence or absence of obesity. Diabetes has also been reported to be more common among hypertensive patients, but this was not demonstrable in our patients with hypertension.

Although hypertension has usually been associated with increased atherosclerosis in both sexes, this has been especially true in women.²⁵ Hypertension in the men in our study was associated with an increased degree of atherosclerosis in their coronary and cerebral vessels, and with a greater occurrence of cardiac catastrophes. This association was even more marked, and involved more arteries, among women with hypertension. These women had more severe atherosclerosis than normotensive women in most of the arteries studied, and in addition had a significantly higher number of cardiac catastrophes. Even though the presence of obesity or hypertension alone was associated with no quantitative difference between the atherosclerosis of men and of women, the presence of both of these diseases in the same patients was associated with a greater increase in atherosclerosis in women than in men.

Other Disease Relationships

The atherosclerosis of patients in our series who had nephrosclerosis was quantitatively similar to that in the patients who had hypertension. Furthermore, as stated above, patients of either sex with nephrosclerosis were significantly more often hypertensive than patients without this disease; and likewise, hypertensive patients had nephrosclerosis a significantly greater number of times than did normotensive patients.

It has been suggested that rheumatic arteritis increases the distribution and severity of coronary atherosclerosis,²⁶⁻²⁸ although other studies have indicated that persons dying of rheumatic carditis have less atherosclerosis than controls.^{29, 30} The patients in our study group who had rheumatic carditis, however, had neither more nor less severe and widespread atherosclerosis than their control patients.

SUMMARY

The incidences of obesity, hypertension, nephrosclerosis, and rheumatic carditis in 500 adult patients were noted at autopsy, and were correlated with the distribution and severity of concomitant atherosclerosis.

In men, obesity uncomplicated by hypertension was associated with a significant increase in the severity of coronary atherosclerosis and the occurrence of cardiac catastrophes. Uncomplicated obesity in women appeared to have no effect upon concomitant atherosclerosis.

Hypertension in men was associated with significantly increased coronary and cerebral atherosclerosis, and with a greater occurrence of myocardial infarction. Hypertensive women had significantly more severe atherosclerosis than normotensive women in most of the arteries studied, and also had significantly more myocardial infarcts.

The atherosclerosis of patients who had nephrosclerosis was similar in distribution and severity to that of patients who had hypertension.

The presence of rheumatic carditis appeared not to influence the extent or severity of concomitant atherosclerosis.

ACKNOWLEDGMENT

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SUMMARY IN INTERLINGUA

Le incidentia de obesitate, hypertension, nephrosclerosis, e carditis rheumatic esseva notate in 500 necropsias de patientes adulte, e le resultados esseva correlationate con le distribution e grados de severitate de atherosclerosis concomitante.

In masculos, obesitate non complicate per hypertension esseva associate con un augmento significative in le severitate de atherosclerosis coronari e le occurrentia de catastrophes cardiac. Obesitate sin complication in femininas pareva haber nulle effecto super le atherosclerosis concomitante.

Hypertension in masculos esseva associate con augmentos significative de atherosclerosis coronari e cerebral e con un plus alte incidentia de infarcimento myocardial. Femininas con hypertension habeva grados significativamente plus sever de atherosclerosis ne femininas normotensive in le majoritate del arterias studiate, e illas etiam habeva un significativamente plus alte incidentia de infarcimentos myocardial.

Le atherosclerosis de pacientes con nephrosclerosis esseva simile in distribution e grado de severitate a illo del pacientes con hypertension.

Le presentia de carditis rheumatic non pareva influentiar le extension o le severitate de atherosclerosis concomitante.

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It has taken long ages of toilsome and often fruitless labour to enable man to look steadily at the shifting scenes of the phantasmagoria of Nature, to notice what is fixed among her fluctuations, and what is regular among her fluctuations, and what is regular among her apparent irregularities; and it is only comparatively lately, within the last few centuries, that the conception of a universal order and of definite course of things, which we term the course of Nature, has emerged.

But, once originated, the conception of the constancy of the order of Nature has become the dominant idea of modern thought. To any person who is familiar with the facts upon which that conception is based and is competent to estimate their significance, it has ceased to be conceivable that chance should have any place in the universe, or that events should depend upon any but the natural sequence of cause and effect. We have come to look upon the present as the child of the past and as the parent of the future; and, as we have excluded chance from a place in the universe, so we ignore, even as a possibility, the notion of any interference with the order of Nature. Whatever may be men's speculative doctrines, it is quite certain that every intelligent person guides his life and risks his fortune upon the belief that the order of Nature is constant, and that the chain of natural causation is never broken.—THOMAS H. HUXLEY. *American Addresses with a Lecture on the Study of Biology*. London, MacMillan and Co., 1877, p. 2.

Work and Heart Disease

II. A Physiologic Study in a Steel Mill

By AMASA B. FORD, M.D., HERMAN K. HELLERSTEIN, M.D.,
AND DAVID J. TURELL, M.D.

Knowledge of the cardiovascular requirements of various types of work is essential in making work recommendations for cardiac patients. In a previous study the stresses of work in a light metal manufacturing plant were shown to be small. The present study is an evaluation of the physiologic requirement of a typical day's work in an open-hearth furnace and other areas in a steel mill. The oxygen consumption, pulmonary ventilation, respiratory rate, and other physiologic responses in cardiac patients are compared to those of normal subjects performing the same tasks.

MUCH of the work in a modern American factory involves little energy expenditure by the worker and evokes only small physiologic changes. Most workers with heart disease are able to perform their jobs in light metal manufacturing plants with no greater evidence of physiologic strain than is shown by their healthy co-workers. These findings in the first part of the present study¹ emphasized the advantages of regular employment for patients with heart disease and showed the stresses of work to be very small—probably less than those of nonworking activities. In heavy industry, however, the energy expenditure and physiologic responses of men with and without heart disease may differ. Our observations have therefore been extended to workers in a steel mill and are reported here.

MATERIALS AND METHODS

There were 53 subjects, of whom 20 had heart disease, 14 were control subjects (a man without clinical evidence of heart disease doing the same job as one with heart disease), and 19 were normal men holding typical steel-mill jobs in which no cardiac subjects happened to be engaged. All the subjects were men. The average age of the

cardiac group was $50 \pm 9^*$ years, which was significantly greater ($p = < .001$)[†] than the control group (34 ± 11 years) or the normal group (40 ± 10 years). There were 3 Negroes among the 20 with heart disease and 7 among the 33 control and normal subjects.

The 20 subjects with heart disease had been identified through employment physical examinations, illness at work, or reports from physicians following illness. All the subjects were evaluated by means of a medical history, physical examination, and standard 12-lead electrocardiogram. Of the 20 men with heart disease, 12 had arteriosclerotic heart disease (9 with previous myocardial infarction confirmed by electrocardiogram), 7 had hypertensive cardiovascular disease, and 1 had a pronounced and unexplained tachycardia. The total cardiac group was distributed according to the classification of the New York State Heart Association³ as follows: Class I, 13 subjects, and class II, 7 subjects; none in classes III or IV (symptoms produced by less than ordinary activity). Therapeutically, 2 were classified A (no restrictions); 17, B (restriction of unusual exertion); and 1, C (moderate restriction of ordinary activities). Men with heart disease were found working in all major areas of the steel mill and at some, but not all, of the most strenuous jobs. Table 1 lists the jobs studied and shows the distribution of the cardiac subjects.

The average body surface area of the steelworkers, as estimated from height and weight, was $1.96 \pm .13$ M.², as compared to $1.86 \pm .15$ M.² for the light metal workers. The average length of service of the subjects studied was 13 years (range, 1 month to 40 years), and there were 17 men who

*Standard deviation.

†† Test for groups of unequal size.²

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had been employed in this mill for 20 years or more.

The subjects were studied at their usual work throughout a typical day's shift by the methods previously reported,¹ with certain modifications. The samples of expired air were collected in butyl rubber bags and analyzed at the plant within 3 hours of collection by a Beckman para-magnetic oxygen analyzer⁴ supplied with a portable vacuum pump. Energy expenditure was calculated according to the formula of Weir.⁵ Radiant heat was measured with a black globe thermometer, air speed with an Alnor "velometer," and wet and dry bulb temperatures with a bulb psychrometer. Heat stress was estimated from the charts of Belding and Hatch,⁶ and values in this report will be referred to as "estimated heat stress."

Data on each subject were entered on punch cards and analyzed by means of a Univac computer. These data included descriptive information (age, diagnosis, etc.), environmental conditions (time breakdown, heat stress, etc.), and physiologic responses, totaling 33 items. Groups of subjects were compared for each parameter by the *t* test for unpaired groups of unequal size. Subjects with heart disease were also individually matched with control subjects performing the same job and compared by the *t*-test for paired groups.⁷

Rates of energy expenditure (calories per minute) are expressed as totals, including resting rates, except as noted in figures 1 and 3.

RESULTS

Job Characteristics

Two major types of stress characterize work in a steel mill: heat and energy expenditure. Figure 1 shows the average energy expenditure and heat-stress index for each of the 5 principal job categories.

Furnacemen. The men who tend the blast and open-hearth furnaces have the heaviest work, such as banking the furnaces and cleaning the runners of cooling slag. As a group, their average energy expenditure for the shift was 3.03 calories per minute (1,435 calories in the shift). The most demanding job in the mill is that of second helper in the open-hearth furnace. The 2 normal subjects studied on this job spent an average of 4.25 and 4.75 calories per minute during the shift. It has been estimated that 5 calories per minute is the maximum tolerable limit of sustained energy expenditure for a healthy man.⁸

TABLE 1.—Types of Jobs Studied

Furnacemen—17 subjects

- A. Blast furnace
 - First helper
 - Water tender—3 subjects**
 - Cinder snapper—2 subjects*
- B. Open-hearth furnace
 - First helper—4 subjects**
 - Second helper—2 subjects
- C. Pouring platform and pit
 - Pourer—2 subjects*
 - First platform man
 - Nozzle setter
- D. Reheat oven
 - Heater helper

Maintenance Men—13 subjects

- Motor inspector—3 subjects**
- Pipefitter—3 subjects**
- Stockman—2 subjects*
- Tool maintenance man*
- Assembler burner
- Boilermaker
- Mason
- Mason helper

Foremen—5 subjects

- General foreman (docks)*
- By-product foreman (coke works)*
- General foreman (coke works)*
- General foreman (blooming mill)—2 subjects

Hot-Strip and Slab Handlers—8 subjects

- A. Hot-strip mill
 - Gauger—2 subjects*
 - Coil marker—2 subjects*
 - Bander
- B. Slab yard
 - Crane follower
 - Stock checker
 - Scarfer*

Controls Operators—9 subjects

- Rougher motor operator—2 subjects*
- Elevator operator (stationary)—2 subjects*
- Scale-breaker operator
- Pit-cover operator
- Tractor operator
- Stripper-crane operator—2 subjects

Miscellaneous—1 subject

- Laborer—shoveling scale

*Each asterisk represents one subject with heart disease.

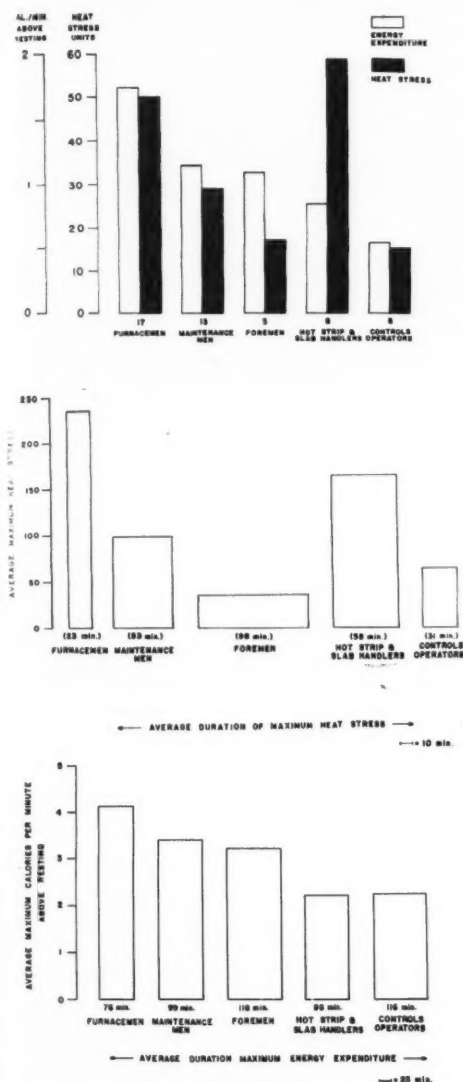


Fig. 1 *Top*. Average energy expenditure (above resting) and estimated heat-stress index⁶ for all subjects in 5 job categories. Standard deviations are of the order of 0.5 calories per minute and 25 heat-stress units.

Fig. 2 *Middle*. Maximum estimated heat-stress index and its cumulative duration during an 8-hour working day averaged for all subjects in 5 job categories.

Fig. 3 *Bottom*. Maximum energy expenditure (above resting) and its cumulative duration during an 8-hour working day averaged for all subjects in 5 job categories.

Most of the men who worked in the furnace areas were, at times, exposed to intense radiant heat. The "heat-stress index"⁶ is an approximate measurement under specific conditions of the balance between the heat load of the unclothed body (radiation, convection, and metabolism) and possible heat loss (radiation, convection, and evaporation of sweat, depending on air temperature and humidity). A heat-stress index of 100 represents a balance of heat load and heat loss of the body at the maximum rate of sweat production.

The furnacemen experienced an average estimated heat stress of 50 during the shift. Every man working in the furnace area was, at some time during the shift, exposed to an estimated heat stress of 140 or more, and three quarters experienced stresses of over 200. Maximum heat-stress conditions are presented in table 2. The 2 second helpers on the open-hearth furnace experienced the highest estimated heat stress (averages of 113 and 116) as well as the highest energy expenditure.

Maximum estimated heat stress and its cumulative duration are indicated in figure 2. Similar data for maximum energy expenditure are presented in figure 3. It is evident that, from a consideration of maximum as well as average energy and estimated heat stresses, the furnacemen had the hardest jobs. The furnacemen walked an average of 5.5 miles per shift with a range of 1.8 to 10.2 miles.

Maintenance Men. The maintenance men ranked second in terms of average energy expenditure (2.58 calories per minute) and third in terms of average heat-stress index (29 units). Their work is more irregular. Maintaining large machinery requires walking, climbing, lifting, and forcing, so that large exertions are required on each shift (fig. 3); but only 2 maintenance men averaged as much as 3.5 calories per minute for the shift. Heat stress was variable but less than that in the furnace areas. The average distance walked in a shift was 2.5 miles.

Foremen. The foremen expended about as much energy (2.48 calories per minute aver-

TABLE 2.—High "Heat-Stress" Conditions of Certain Jobs in the Furnace and Strip-Mill Areas

Job	Second helper	First helper	"Cinder snapper"	Gauger
Area	Open-hearth furnace	Open-hearth furnace	Blast furnace	Strip mill
Activity	controlling "tap" of molten steel	banking furnace	controlling "cast" of molten iron	gauging coil of hot steel
Globe temperature (radiant heat) (°C.)	160	95	165	142
Wet-bulb temperature (°C.)	28.3	24.5	18.3	22.8
Dry-bulb temperature (°C.)	39.3	34.5	25.0	35.5
Air speed (ft./min.)	50	350	100	850
Metabolic heat production (cal./min.)	4.7	6.1	2.6	2.9
Cumulative duration of exposure to these conditions during shift (min.)	78	57	3	15
Heat-stress index ^a	over 250	220	over 250	over 250

age) as did the maintenance men. The majority of this energy was spent in walking an average of 4.5 miles per shift, but neither distance walked, maximum, nor average energy expenditure approached that of the furnacemen except in the case of one vigorous 24-year-old temporary foreman who averaged 3.9 calories per minute and walked 7.5 miles. The foremen seldom encountered sustained severe heat stresses.

Hot-Strip and Slab Handlers. These jobs involve the handling, marking, or measuring of hot steel, either as slabs or coils of sheet steel. The average energy expenditure of 2.12 calories per minute is unimpressive, being less than twice the average resting level, and there are few high peaks. The stress of this work comes from the radiant heat of large masses of hot steel producing the highest average estimated heat stress of all the jobs studied (59 units) but not reaching the dramatic peaks experienced by the furnacemen during a tap (table 2). These men walked an average of 1.2 miles.

Controls Operators. Workers in this group drive machinery from a sedentary position, either moving with the machine (tractor and crane) or remaining stationary (scale breaker, pit cover). Their average energy expenditure (1.81 calories per minute) and estimated heat stress (15 units) are the lowest of any group, and they seldom show significant peaks. The crane cabs and operating "pulpits" are air-conditioned in hot areas.

Work and Rest Time. The proportion of working to nonworking time was quite uniform throughout the mill, except for the foremen, who rested only 29 per cent of the shift, as compared to 41 per cent for the furnacemen, 42 per cent for the hot-strip handlers, 48 per cent for the controls operators, and 54 per cent for the maintenance men. These figures represent the fraction of time between check-in and check-out not actually spent at work and include meals, changing clothes, and breaks, both voluntary and routine. In light metal manufacturing plants, nonworking time accounted for 35 per cent of the shift.

Physiologic Responses of Normal and Cardiac Workers

Pulse Rate. The resting pulse rate rose from an average for the total group of 77 ± 12 beats per minute before work to 90 ± 13 at the end of the shift. This change was statistically significant ($p = <.001$) in the cardiac, control, and normal groups. The men with heart disease showed a higher average resting pulse rate throughout the day than did their matched controls (fig. 4). The differences, averaging 9.4 beats per minute, were significant statistically ($p = <.05$). Among the cardiac subjects, those with hypertension tended to have higher resting pulse rates than did those with arteriosclerotic heart disease although the differences were significant only at the end of the shift ($p = <.05, <.02$) (fig. 5).

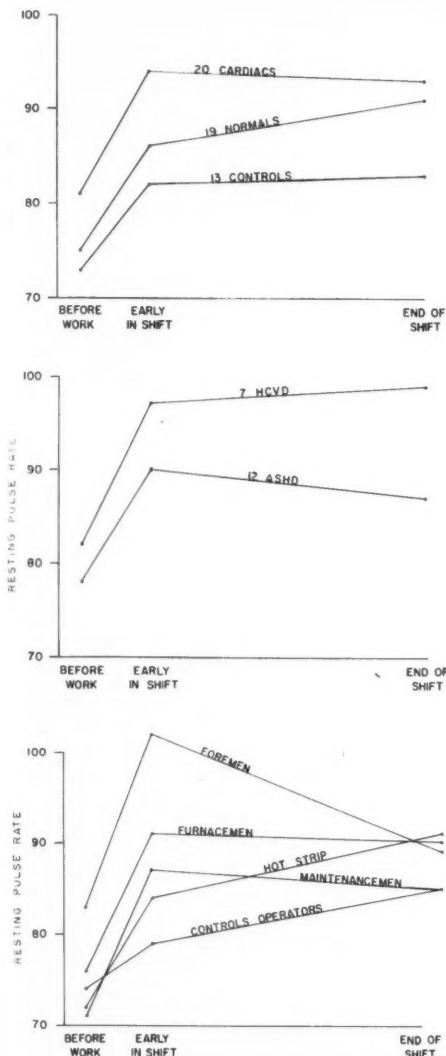


FIG. 4 *Top*. Average resting pulse rate at 3 points during the shift for cardiac, control, and normal subjects. Standard deviations are of the order of 12 pulse beats per minute. "Early" refers to the first pause after starting work (within the first hour).
 FIG. 5 *Middle*. Average resting pulse rate at 3 points during the shift for subjects with hypertensive and arteriosclerotic heart disease. Standard deviations are of the order of 12 pulse beats per minute.
 FIG. 6 *Bottom*. Average resting pulse rate at 3 points during the shift for all subjects in 5 job categories. Standard deviations are of the order of 12 pulse beats per minute.

Eighty-five per cent of the rise in average resting pulse rate occurred within the first hour of the shift, although this pattern varied from one type of job to another. Figure 6 shows that the foremen experienced a striking rise in resting pulse during the first pause after starting work (within the first hour) with a subsequent fall, whereas the hot-strip and slab handlers and controls operators showed a gradual rise during the shift, and the other jobs conformed to the general pattern. These differences may be related to the fact that the foreman's job is unpredictable, with a high degree of responsibility, while the controls operators and hot-strip and slab handlers have the most routine type of work, suggesting that the resting pulse rate increases early when anxiety-producing factors are present. The pattern of average resting pulse rate did not correlate with average energy expenditure or heat stress.

Maximum working pulse rates of 140 per minute or higher were observed in 17 of the 53 subjects (8 with heart disease, 9 without). In 14 of the 17, tachycardia (140 to 170) could be accounted for by energy expenditure (>4 calories per minute) or estimated heat stress (>200). Three men with hypertension developed pulse rates of 140 to 168 per minute, which were not the result of their energy expenditure or heat stress and which might therefore be considered excessive. The fourth individual had an unexplained tachycardia, with an average resting pulse rate of 120 per minute and a maximum of 212 per minute.

There is a rough correlation between rate of working energy expenditure and pulse rate at low heat stress. At high heat stress, the pulse rate tends to be higher for a given rate of energy expenditure (fig. 7). Factors influencing the working pulse and recovery pulse sum (total beats in 3 minutes after work) were studied by analysis of variance, using heat-stress index, energy expenditure, and age as the "treatments."² There were 2 replications of 8 normal subjects each. Heat-stress index was related to both working pulse rate and recovery pulse sum, and this relation was statistically significant at the 5 per

cent level. The influences of energy expenditure and age were not statistically significant. Other studies have shown a correlation between heart rate and energy expenditure,⁹ but this effect is overshadowed under working conditions in a steel mill—particularly by the effect of high heat stress.

Pulse rate, under working conditions in a steel mill, is therefore influenced by heat load and energy expenditure and by the individual characteristics of the worker, particularly those of heart disease and anxiety.

Blood Pressure. Few marked elevations of blood pressure were observed. It was difficult to obtain satisfactory blood pressure readings during work because of noise, activity, and protective clothing. Observations were made immediately after work or during stationary activity, while the pulse rates were recorded by electrocardiograph during work.

Sixteen individuals developed blood pressures greater than 150 mm. Hg systolic or 99 mm. Hg diastolic or both. Seven of these had hypertension at rest, and 4 had arteriosclerotic heart disease with elevated or borderline resting blood pressure. Five men without recognized heart disease developed systolic pressures in the range of 154 to 160 mm. Hg or diastolic pressures as high as 100. Three of these otherwise normal subjects had borderline systolic blood pressures at rest (140 to 160 mm. Hg).

The maximum increase during, or immediately following, work averaged 6 mm. Hg systolic and 3 mm. Hg diastolic for the 33 noncardiac subjects. These changes were no greater in high heat stress, at high rates of energy expenditure plus high heat stress, or for the men with arteriosclerotic heart disease. Only the 7 hypertensive subjects showed a greater average increase of blood pressure, and then only of systolic pressure (11 mm. Hg).

Thus, the blood pressure data suggest that within the limits of the observations, most steel-mill workers experience only moderate increases in blood pressure, but that certain individuals, some with recognized hypertension and some not, have a more exaggerated

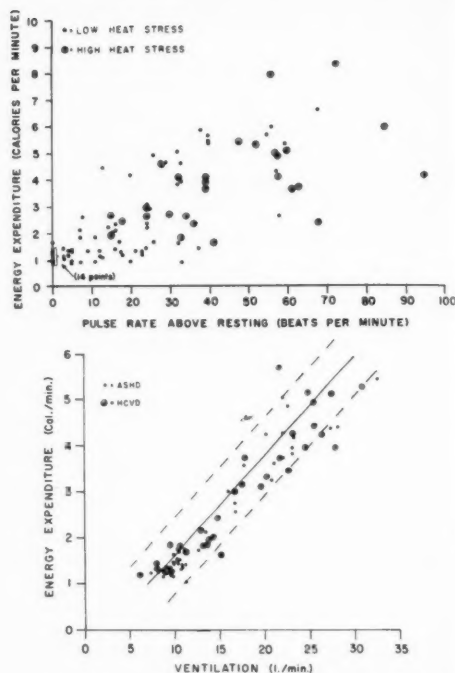


Fig. 7 Top. Energy expenditure and pulse rate during individual activities for 33 normal and control subjects. Solid dots represent low heat-stress activities (20 units or less) and circled dots represent high heat-stress activities (100 units or more).

Fig. 8 Bottom. Energy expenditure and pulmonary ventilation during individual activities for 7 subjects with hypertensive heart disease (circled dots) and 12 subjects with arteriosclerotic heart disease (solid dots) at normal heat stress (less than 60 units). The solid line represents the average for noncardiac subjects and the dashed lines ± 2 standard deviations.

elevation of blood pressure under the same working conditions.

Respiration. Pulmonary ventilation, on the other hand, is so closely correlated with energy expenditure and so uniform in groups of normal individuals that one quantity may be predicted from the other. The data of this and previous studies have been analyzed for this correlation.¹⁰

The correlation between ventilation and energy expenditure is not affected by the presence of heart disease (fig. 8) or by high heat stress (fig. 9). The average pulmonary ven-

TABLE 3.—*Electrocardiographic Changes During Work*

Case	Diagnosis	Age	Activity	Electrocardiographic changes
A normal electrocardiographic changes during work				
S.W.	normal	46	nozzle setting 5.3 cal./min., heat stress 300	nodal premature beats, aberrant conduction; 45° counterclockwise shift T-vector
R.T.	arteriosclerotic heart disease, non- transmural anterior infarction	45	shoveling, smoking, etc.	S-T segment depression of 1 mm.; 120° clockwise shift T-vector
J.B.	arteriosclerotic heart disease, right bundle branch block	64	running up stairs (emergency)	ventricular premature beats
R.B.	sinus tachycardia	54	walking	S-T segment depression of 1mm., pulse rate 120-212
B borderline electrocardiographic changes during work				
D.H.	normal	28	shoveling 4.8	S-T segment depression of 2mm.
S.K.	hypertensive cardiovascular disease	38	cal./min. walking	(junctional) 60° counterclockwise shift T-vector

tilation at rest was 9.9 ± 2.1 L. per minute, and the average peak was 24.6 ± 6.6 L. per minute for the total group.

Respiratory rates averaged 17 ± 4.0 per minute at rest for the total group, and the average of maximum rates was 26 ± 6.0 . There was no difference between the cardiac and control groups in this respect.

Pulmonary ventilation and respiratory rate, therefore, appear to be influenced primarily by energy expenditure and very little by heat or individual characteristics such as the presence of compensated heart disease.

Electrocardiogram. Standard 12-lead electrocardiograms were taken at rest. Of the 12 subjects with arteriosclerotic heart disease, 9 had evidence of old myocardial infarctions (1 posterior, 4 lateral or anterolateral, and 4 anteroseptal), 2 had complete right bundle-branch block, and 1 had a normal electrocardiogram but a definite history of angina pectoris. None was taking digitalis, and 2 used nitroglycerin occasionally. Of the 9 subjects who had hypertensive cardiovascular disease, 4 showed left ventricular hypertrophy and 3 had normal electrocardiograms. Among the hypertensive group, none was taking digitalis, and 1 was taking antihypertensive medication. The electrocardiograms of the control subjects were all within normal limits.

For the records taken during activity, the method of electrode placement gave information only in the horizontal plane, i.e., on the

x and z axis, equivalent to RV_8 , V_4 , and V_8 . Four men developed changes during or following effort that could be interpreted as an abnormal response, and 2 developed borderline changes. The criteria are those developed for interpreting the Master 2-step test.¹¹ The details are given in table 3. Two of the 6 showing changes had no recognized heart disease but were working at a high rate of energy expenditure (both) and high estimated heat stress (case S.W.). For the 4 men with heart disease, the activities that produced changes were only moderately strenuous.

Abnormal electrocardiographic changes, like the hypertensive response, appear to be characteristic of an individual. High heat stress or high rates of energy expenditure can bring out electrocardiographic changes in an individual not known to have heart disease, but these stresses, even at the levels encountered in the steel mill, did not induce electrocardiographic abnormalities in most normal individuals nor even in 80 per cent of those with known heart disease.

Multiple Abnormal Responses. An unusual increase in blood pressure, abnormal electrocardiographic changes, and tachycardia not explained by energy expenditure or heat stress have been shown to be characteristic responses of an individual rather than necessary effects of heat or physical activity. Thirty-five per cent of the cardiac group and 10 per cent of the noncardiac group showed

TABLE 4.—*Subjects with Abnormal Responses of Pulse Rate, Blood Pressure, and Electrocardiogram*

Job	Diagnosis	New York State Heart Association classification	Age	Excessive tachycardia	Excessive increase of blood pressure	Abnormal electrocardiographic changes
Motor inspector	malignant hypertension	II	42	+	+	
Pipefitter	hypertensive cardiovascular disease	II	33	+	+	
Water tender	arteriosclerotic heart disease, right bundle-branch block	I	64	+	+	
First helper, open-hearth furnace	arteriosclerotic heart disease, non-transmural anterior infarction	II	45	+		+
Foreman	unexplained tachycardia	I	54	+		+
Pipefitter	hypertensive cardiovascular disease	I	38		+	B*
"Cinder snapper," blast furnace	hypertensive cardiovascular disease	I	49	+	+	
Mason	normal		42	+	+	
Nozzle setter	normal		46			T
Laborer	normal		28			B

*Borderline.

2 or more such abnormalities or electrocardiographic changes alone (table 4). The significance of these findings can be determined only by follow-up observation.

At the time of writing, a year and a half had passed since the conclusion of this study, and only 1 subject was known to have died. He was 41 years old and had had a myocardial infarction 3 years previously. On returning to work he was transferred from heavy work in the blast furnace to the job of stockman, which required only 2.25 calories per minute during the shift with a peak of 4.40 calories per minute (stair climbing). He died suddenly at home 5 weeks after the study. An autopsy was not performed. During the study he did not develop any of the abnormalities cited above.

Effects of Heat Stress. The outstanding cardiovascular effect of heat stress noted so far has been acceleration of heart rate. This occurs concomitant with an increase in cardiac output and peripheral blood flow through dilated skin vessels where heat loss takes place by radiation and convection. The principal means by which the body loses heat, however, is evaporation of sweat. In the present study,

observations were made of water ingestion by 12 subjects working at average heat-stress indices of from 25 to 130. When water intake was plotted against average heat-stress index, a rough correlation was evident that could be described by a line crossing the heat-stress index = 100 line at 0.52 L. of water per hour. This is about half the sweat production predicted by Belding and Hatch for these working conditions.⁶ The discrepancy can be explained by 2 factors. First, the sweat secretion of the subjects may have exceeded their water ingestion, resulting in a weight loss. Nude weights could not be taken in this study. Second, the heat-stress index may not represent the actual conditions to which the subjects' bodies were exposed. This index is based on observations on nude or minimally clad subjects whereas steel-mill workers wear heavy clothing, often including an asbestos overcoat. Clothing reflects radiant heat and may impede or facilitate sweat evaporation, but diminishes heat loss by convection. The most important effect of clothing in the high radiant heat areas appears to be to shield the body, thus reducing the stimulus to sweat secretion and reducing the true heat stress.

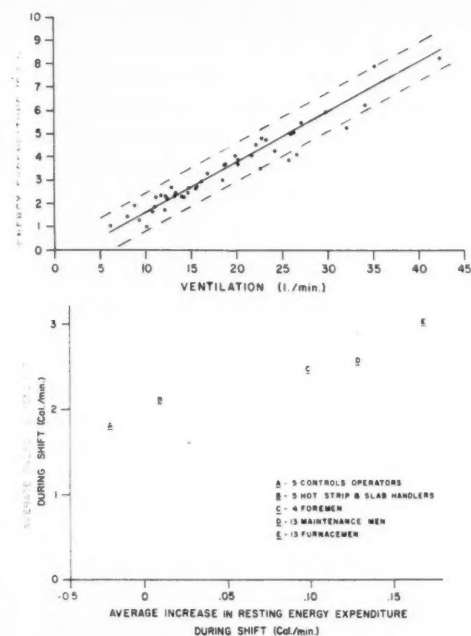


FIG. 9 *Top*. Energy expenditure and pulmonary ventilation during individual activities at high heat stress (greater than 60 units) for 33 noncardiac subjects. The solid line represents the average for these same subjects at low heat stress, and the dashed lines ± 2 standard deviations.

FIG. 10 *Bottom*. Average energy expenditure during the shift related to average increase in resting energy expenditure during the shift for 40 cardiac and noncardiac subjects.

below the level indicated by the heat-stress index.

Fatigue. There was an increase in the average resting energy expenditure from $1.34 \pm .14$ calories per minute before work to $1.45 \pm .12$ calories per minute at the end of the shift for the total group. This increase was small but statistically significant ($p = <.01$). The increase was no greater for the cardiac group than for those without heart disease. When the increments were broken down by type of job, however, there appeared to be a correlation between the average rate of energy expenditure for the day and the increase in resting metabolic rate during the shift (fig. 1). The increments are small, and there is considerable variation, so that the correlation

is not statistically significant in the present data. It appears, nevertheless that in the jobs that require an average energy expenditure of 2.5 calories per minute or more, there may be a small but detectable increase in resting metabolic rate, which represents one form of physiologic fatigue.¹³

Resting pulse rate also rose during the shift (fig. 4). The rate of energy expenditure is only one of the factors contributing to this rise. Heart disease, anxiety, and heat stress all have important influences, as has been demonstrated. The increase in pulse rate for various groups does not correlate with their energy expenditure. There is, however, a rise in every group, regardless of the presence or absence of other influences. It is possible that a rise in resting pulse rate takes place during the day's work in a steel mill which also represents fatigue, but which is difficult to dissociate from the effects of heat stress, heart disease, and anxiety.

COMPARISON OF CARDIAC AND CONTROL SUBJECTS

The men with heart disease were compared with their matched control subjects in order to identify significant differences that might be due to heart disease itself or, indirectly, to a modified pattern of activity resulting from heart disease. Most of the important differences have been cited. Thus, the men with heart disease had slightly higher resting pulse rates, but their working pulse rates were not significantly greater, except in occasional individuals, than those of the control subjects. Resting blood pressures were greater in the cardiac group and increased more during work. Both pulse rate and blood pressure differences were more accentuated in the hypertensive group than in those with arteriosclerotic heart disease. Twenty per cent of the cardiac subjects and 6 per cent of those without heart disease developed borderline or abnormal electrocardiographic changes at work.

Perhaps the most striking fact that emerges from the comparison of the cardiac group with their healthy co-workers is that there are many jobs in a steel mill which are performed

satisfactorily by men with recognized heart disease and that men with heart disease are actually working at jobs of every general type and in every area in the mill. There were no cardiac subjects on the hardest job, that of second helper on the open-hearth furnace, but otherwise, there was a wide distribution (table 1). The sample is not a weighted one, but most of the important jobs are represented.

There is some evidence that the high energy cost of certain jobs in the steel mill may elicit abnormal physiologic responses in men with known heart disease and, occasionally, in men without recognized heart disease. All but 2 of the workers listed in table 4 as showing such changes were in the furnace or maintenance groups, and these 2 groups had the highest average energy expenditure. It is to be emphasized that there is no evidence in this study that these changes were actually harmful to the men who experienced them.

The general pattern of energy expenditure was not found to differ significantly when the cardiac subjects were compared with their controls. Resting energy expenditure, average energy expenditure during the shift and during actual work, maximum energy expenditure, and the proportion of resting to working time—none of these measurements could be shown to differ significantly or consistently between individuals with and without heart disease. This statement stands even in references to comparisons within the furnaceman and maintenance man groups, which had the highest energy expenditure.

COMPARISON WITH OTHER STUDIES

Comparison of the present study with similar observations in Europe indicates that American steelworkers expend less energy and work a smaller proportion of the shift than comparable workers in Europe.

Christensen and his co-workers have made a study of physiologic changes in normal subjects during work in a Swedish steel mill.¹⁴ They reported that the energy cost of 4 jobs* (slag removal, dolomite shoveling, tending the heating furnaces, and wire bun-

dling) averaged over 10 calories per minute whereas in the present study the 2 heaviest jobs studied were slag removal (8.3 calories per minute) and shoveling dolomite (7.1 calories per minute). The impression that some jobs actually are harder in Sweden is strengthened by the fact that their study reported 8 jobs at which pulse rates of over 170 were observed and 2 (hand rolling and wire bundling) where the working pulse rate averaged 181 and 183, whereas the present study included only 1 worker whose pulse rose above 170 (the subject with a resting tachycardia). The discrepancy is probably due to the use of more mechanized equipment in the American steel mill. For example, the manual part of lining the open-hearth furnace with dolomite (shoveling) takes 3 men 15 to 20 minutes in the Swedish mill, whereas the operation is almost entirely done by machine in the American mill. Another example is "hand rolling" of hot ingots between passes through the rolling mill—one of the most strenuous jobs in the Swedish study. In the American mill, this operation is accomplished by a seated operator in an air-conditioned control "pulpit."

Studies in iron and steel tempering foundries of West Germany,¹⁵ although concerned with somewhat different work, show a greater proportion of workers expending large amounts of energy. Thus, 5 out of 15 workers in a German foundry spent over 2,000 calories per shift, compared to 2 out of 53 in the present study. The German workers also rested an average of 20 per cent of the shift, while the steelworkers of the present study rested 45 per cent of the shift.

The energy expenditure of the furnacemen in the present study averaged 1,435 calories for the shift (range 800 to 2,290 calories). According to the studies and calculations of Lehmann, comparably strenuous jobs outside the metal industry are as follows: in agriculture, Alpine dairyman, Mosel wine grower and Hungarian harvest hand; in mining, coal

*"Jobs" here refer to single activities rather than types of employment.

enter and manual mover; in the stone and earth industry, kiln loader, building stone enter, and limestone loader; and, in other fields, blacksmith, lumberjack, railway maintenance man, coal passer, and laborers at tasks such as carrying sacks of flour.¹⁶

The steelworkers of the present study differed markedly from the workers in light metal manufacturing plants previously studied from this laboratory.¹ The steelworkers, in general, expended more energy (1,190 vs. 997 calories per shift), but worked less of the shift (55 vs. 65 per cent of the shift). Many jobs in the steel mill entailed high estimated heat stress, and many of these also required high energy expenditure. Higher rates of pulse and oxygen consumption were observed in the steel mill, and there were somewhat more frequent electrocardiographic changes, but observed increases of blood pressure were no greater.

It is important to note that in every work area of the steel mill, except the blast furnace and open-hearth furnace, there were jobs requiring low rates of energy expenditure comparable to those found in the light metal plants (average energy expenditure for the shift of less than 2 calories per minute).

Finally, the elevation of resting energy expenditure (oxygen consumption) and pulse rate at the end of the shift suggests a type of physiologic fatigue in the steelworkers that was not found in the light metal workers.

SUMMARY

Fifty-three steelworkers, 20 of whom have heart disease, have been studied during a typical day's work. In certain jobs, particularly in the open-hearth and blast-furnace areas, workers expended an average of 3 to 4 calories per minute during the shift, and 2 approached the estimated physiologic tolerance limit of 5 calories per minute. Estimated heat stresses in the furnace areas and close to hot steel were often high, although jobs were also studied that had low energy requirements and negligible heat stress.

Men with hypertensive and arteriosclerotic heart disease were found working at jobs of

many types, and they expended energy at the same rate and worked the same proportion of the shift as normal men. Seven of the 20 cardiac and 3 of the 33 presumably normal men developed either abnormal electrocardiographic changes or increases in pulse rate and blood pressure that appeared excessive for the working conditions.

Oxygen consumption, pulmonary ventilation, and respiratory rate under these conditions varied primarily with energy expenditure. Fluid intake depended on heat stress. Blood pressure increased with energy expenditure but was more influenced by individual characteristics such as hypertension. Pulse rate was regulated in a more complex fashion than any of the other parameters, being markedly increased by heat stress but also measurably influenced by energy expenditure, the presence of heart disease, and probably anxiety. Electrocardiographic changes during work were also characteristic of the individual rather than of a particular stress. There was a slight but significant increase in resting pulse rate and resting metabolic rate during the shift consistent with development of physiologic fatigue.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Cinquanta-tres acieristas, incluse 20 con morbo cardiac, esseva studiate in le curso de un typic die de travalio. In certe typos de travalio—specialmente in le areas del furnos a soela e del alte furnos—le homines dispendeva, al media, 3 a 4 calories per minuta durante le giornata, e 2 approchava le estimate limite de tolerantia physiologic de 5 calorias per minuta. Le estimate stresses de calor in le areas del furnos e alteremente in le proxi-

mitate de acciaio calide esseva alte in multe casos, ben que le studio includeva etiam typos de labor con basse requirements de energia e negligibile stresses de calor.

Homines con morbo cardiac hypertensive e arteriosclerotic esseva incontrate in occupationes de multe differente typos, e illes expendeve energia al mesme mesura e illes travaliava le mesme proportion del jornada como homines normal. Septe del 20 cardiacos e 3 del 33 presumimente normal subjectos in le studio disveloppava anormalitates electrocardiographic o anormal augmentos del frequentia del pulso e tensiones de sanguine que pareva esser excessive pro le conditiones de labor con que illos esseva associate.

Le consumption de oxygeno, le ventilation pulmonar, e le frequentia respiratori variava sub iste conditiones primariamente con le expensa de energia. Le ingestion de liquido dependeva del stress de calor. Le tension de sanguine montava con le expensa de energia sed esseva influentiate plus marcatamente per characteristicas individual como per exemplo le presentia de hypertension. Le frequentia del pulso esseva regulate de maniera plus complexe que omne le altere variabiles. Illo esseva augmentate marcatamente per stress de calor, sed illo esseva etiam influentiate mesurabilemente per le expensa de energia, le presentia de morbo cardiac, e, probabilemente, le presentia de anxietate. Le alterationes electrocardiographic que occurreva durante le travaglio esseva similimente characteristic del individuo plus tosto que del presentia del un o del altere typo de stress. Esseva notate un leve sed significative acceleration del pulso in stato de reposo e del metabolismo in stato de reposo in le curso del jornada in association con le disveloppamento de fatiga physiologic.

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Digitalis Delirium

A Report on Three Cases

By GERARD CHURCH, M.B., CH.B., AND HENRY J. L. MARRIOTT, M.D.

ALMOST a century ago Duroziez¹ first used *delire digitalique* to describe mental disturbances that he attributed to digitalis intoxication. Like myxedematous madness, the term digitalis delirium is an alliterative and euphonious "burr that sticks in the memory." The word delirium, literally a wandering from the furrow (*L. lira*), has become more specific than madness and is properly applied to an agitated form of acute confusional psychosis. Duroziez did not define his use of the term, and King,^{2,3} in his review of digitalis delirium in 1950, included degrees of mental disturbance varying from calm disorientation to violent psychosis. As the term is euphonious and memorable, its continued use in this wider sense seems justifiable.

Despite its recognition 90 years ago and King's recent thorough review of the subject, and despite the fact that "dementia produced by digitalis" has been upheld in the law courts in defense of homicide,⁴ the subject has not received much attention. Although reports of intoxication with digitalis preparations have been numerous, instances of toxic psychosis have been few; furthermore, in some of these, the drug has not been clearly incriminated. Recently 3 carefully studied cases of digitalis delirium were seen at the Mercy Hospital.

CASE REPORTS

Case 1

J.M.C., a white man aged 83, had been in excellent health until 2 weeks prior to his admission, when he developed a head cold, chest infection, and subsequently congestive heart failure of moderate degree. There was no history from the patient

or his relatives of alcoholism or mental illness. He presented physical signs of aortic insufficiency and examination of his central nervous system was negative. The serologic tests for syphilis were positive. He responded rapidly to therapy with bed rest, low-sodium diet, antibiotics, gitalin, and diuretics. His permission was obtained to keep him in hospital and to include him in a study of digitalis intoxication.

All therapy was withheld except for a 2-Gm. sodium diet and a digitalis preparation. Starting with gitalin, he received 15 mg. over 7½ days. At this point drowsiness, anorexia, nausea, and vomiting appeared and the drug was stopped. His symptoms improved in 48 hours and, after 6 days rest, digoxin was given. He received 2.5 mg. over 36 hours, but then he developed anorexia, nausea, and vomiting. An electrocardiogram showed paroxysmal atrial tachycardia with varying atrioventricular block. Within 24 hours of stopping of digoxin his symptoms had improved and his heart rate was 80 per minute. The electrocardiogram indicated restoration of sinus rhythm. After a 4-day rest period, digitoxin was administered in dosage of 1 mg. in the first 24 hours and then 0.1 mg. at 8-hour intervals. After a total dose of 3.1 mg. over 8 days he became disoriented and wildly excited, stated that he was in a brewery, and repeatedly demanded beer. Restraints and sedation with paraldehyde were necessary, but after 36 hours he became his usual self. There was no alteration in his pulse rate to suggest an arrhythmia and an electrocardiogram taken soon after he had recovered showed sinus rhythm and first degree atrioventricular block. He had apparently complained of slight nausea to a nurse before his last dose, but this had not been reported to the medical staff. Throughout the trial there was no diuresis and no electrolytic abnormality.

He was discharged and followed as an outpatient on digoxin 0.25 mg. twice daily for 9 months. During this time his clinical picture was one of fluctuating congestive heart failure. Eventually he was readmitted with edema and other evidence of congestive heart failure associated with blurring of vision and white spots in his visual fields. He received treatment with a low-sodium diet and diuretics; digitalis was withheld as digoxin intoxication was suspected. After 5 days, im-

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provement had occurred and only minimal evidence of congestive failure remained. He was given 0.5 mg. digitoxin in 1 dose and 0.1 mg. 8 hourly thereafter. After 11 days he had received 3.5 mg., when he developed anorexia, nausea, and vomiting. First degree atrioventricular block was noted by electrocardiogram, but no change in electrolytes had occurred. Two to 3 days after stopping the drug, the patient's symptoms disappeared.

Comment. In this case, delirium occurred as the earliest convincing manifestation of intoxication with digitoxin. Previously other digitalis preparations pushed to early toxicity had not produced mental symptoms and subsequently digitoxin itself did not reproduce it.

Case 2

A.R., a Negro aged 57, had been under treatment for 15 years with salt restriction, digitalis preparations, and diuretics for congestive heart failure. His cardiac lesion was aortic insufficiency and he had a positive serologic test for syphilis. He had no signs of neurologic involvement and, although of a rather gloomy nature, the patient had been found cooperative and friendly at out-patient attendance. No history of mental disorder or alcoholism was obtained from him or his friends (he had no relatives). As an out-patient he was being maintained on 1 mg. of digoxin daily, but during the 14 days prior to admission, his condition deteriorated and on admission there was evidence of severe congestive heart failure. He was treated with oxygen, venesection, salt restriction, digoxin (1 mg. daily), mercaptopurin and chlorothiazide. He responded rapidly and after 14 days he was free of edema, his liver had decreased in size, and his lung fields were clear.

All therapy other than a 2-Gm. sodium diet was withheld and then digoxin 0.5 mg. 3 times daily was started. After 8 days he developed anorexia, palpitation, dizziness, and blurring of vision, and his pulse, previously regular, developed occasional dropped beats. An electrocardiogram showed sinus rhythm with occasional ventricular premature beats and first degree atrioventricular block. Through a misunderstanding he was given an additional 1.5 mg. of digoxin during the following 24 hours and thereafter he became restless and irritable. He insisted on being isolated with the curtains drawn around his bed as he claimed the other ward patients were making a fool of him. The following day he developed overt paranoia; he complained that the nurses were after him with knives and that the patient in the next bed was about to attack him with his crutch; he would look warily over his shoulder for an assault from the rear and, suspicious of poisoning, he refused food and drugs.

Restraints became necessary at night when he refused to stay in bed. In conversation he was confused about his home circumstances and in his actions he was hesitant and indecisive. Such behavior patterns continued in varying degree for 14 days; after 9 days he started eating, but as late as the fourteenth day he barricaded himself in a side room to which he had been moved. On this occasion he required restraint and heavy sedation. His pulse became regular 4 days after digoxin was stopped and an electrocardiogram indicated sinus rhythm with no premature beats. After 14 days improvement set in and at the end of 3 weeks his behavior and train of thought had been normal for 5 days. During the third week after digoxin had been stopped, evidence of heart failure reappeared. This responded to mercaptopurin and chlorothiazide. Throughout the period of psychosis, no abnormality in his serum electrolytes occurred and his treatment included sedatives, small doses of insulin to stimulate appetite, mercaptopurin, and chlorothiazide.

After discharge he was followed as an out-patient and, when congestive failure recurred, control was at first achieved by diuretics, but after 6 weeks digoxin was restarted in doses of 0.25 mg. twice daily. There was no further occurrence of toxicity or mental disorder during the following 4 months. Finally, when he failed to report for review, it was discovered that he had died suddenly at home.

Comment. The alarming feature of this case was the duration of the delirium which occurred with 1.5 mg. over the minimal intoxicating dose. Manifestations of intoxication with the short-acting glycosides usually disappear within 48 hours, but exceptions do occur and are mentioned later. It is of further interest that delirium persisted long after other signs of intoxication had disappeared.

Case 3

S.A., a white man aged 65, was admitted to the Mercy Hospital with a history of recurrent breathlessness on exertion, palpitation, and ankle swelling of 5 years' duration. He received digitoxin, gitalin, and occasional diuretics. He gave no history of mental illness, but admitted to being a heavy drinker prior to the last 3 or 4 years. On admission he showed obesity, cyanosis, distention of the neck veins, marked pitting edema, and fever of 101 F. The patient was alert, cooperative, and well oriented. The blood pressure was 166/82 mm. Hg, the pulse was 160 per minute and completely irregular, and the heart was enlarged to the left. Crepitations were audible at the lung bases. The liver was palpable 6 cm. below the costal margin and was firm and slightly tender. Examination of

TABLE 1.—Laboratory Data in Case 3

Day in hospital	Urea (mg. %)	S.G.O.T. units	Bilirubin (mg. %)	Thymol	Albu- min	Globulin	Total	Na	K	CO ₂	Cl	
			Total	Direct	units	(Gm. %)	protein		(mEq./L.)			
2-7	76	145	1.5	0.5	5	3.1	3.6	6.7	138	5.2	21	97
9	145		2.8	1					133	5.08	20.3	95.6
11	172	108							138	5.56	20.7	105.1
13	176								138	4.35	17.5	96.7
15	142	30	2.2	0.9	4	3.1	4.2	7.3	142	5.14	18.8	97.0
17	99											
20	64											
21		35	1.9	0.9	4	3.3	3.8	7.1				
22	42											
24			1.4	0.6		3.1	3.6	6.7	128	3.52	20.7	92.9
25		40							138	4.46	20.3	107.1
26	63											
29	42								133	4.96	20.7	97.9

the central nervous system was normal. His prostate was enlarged and the urine contained 4+ albumin, but no cells or casts. The other laboratory data are shown in table 1. The electrocardiogram showed atrial fibrillation and nonspecific ST-T changes. An x-ray of the chest showed considerable left ventricular enlargement and passive congestion of the lung fields.

A diagnosis was made of coronary artery disease with heart failure precipitated by an infection of undetermined site. It was also thought probable that the patient had cirrhosis of the liver and prostatic hypertrophy. Recent myocardial infarction was considered unlikely. The patient was treated with a low-sodium diet, mercaptopurin, chlorothiazide, and penicillin. After initial digitalization with lanatoside-C, 1.2 mg., followed by gitalin, 7 mg. over 3 days, the patient was maintained on gitalin 0.5 mg. daily. A diuresis occurred with improvement in the signs of failure including loss of edema and loss of 20 pounds in weight, but a recurrent pyrexia up to 101 F. continued.

On the eighth hospital day he developed a chill and a temperature of 106 F. was recorded. His urinary output fell to 80 ml. in 24 hours; then a diuresis followed, but on the sixteenth day the output again decreased to a daily total of between 200 and 900 ml. A urinary tract infection, complicated by bacteremia, peripheral circulatory failure and a low-grade pyrexia, was responsible.

The patient became somewhat lethargic with short spells of confusion during the 8 days following his hyperpyrexia and, parallel with the decline in his urinary output, he became more persistently confused and disoriented with periods of aggressive behavior. No improvement was noted upon

use of an oxygen tent. Later he developed visual hallucinations. His appetite, poor since admission, became worse and vomiting started on the seventeenth day gradually increasing in frequency over the next 5 days. On the twenty-first day he was incontinent of urine, hallucinating, and vomiting frequently. Intravenous fluids were commenced. On the twenty-second day a bigeminal pulse was noted and the electrocardiogram showed ventricular bigeminy. This focused attention to gitalin which had been given continually since admission; when it was withheld, improvement occurred dramatically within 48 hours. The patient became alert and cooperative, his appetite returned, and nausea, vomiting, and bigeminal rhythm were no longer noted. No further disturbance of mental behavior occurred. His cardiac status remained fairly well compensated on digoxin 0.25 mg. daily, which was instituted 1 week after omission of gitalin.

Comment. In this case, delirium occurred in the presence of other possible etiologic agents besides digitalis. Severe infection, hepatic failure, uremia secondary to renal failure, and electrolyte imbalance could have been responsible. As the delirium became worse, however, tests of hepatic function improved and the blood urea fell; moreover, little or no increase in his urinary output coincided with the dramatic improvement in his symptoms. The evidences of severe infection developed and disappeared before his delirium reached its peak, and the low-grade pyrexia, which developed later, persisted after improvement had occurred. Electrolyte imbalance was possibly present but, considering the progression, the associated gastrointestinal disturbances and the bigeminy, the weight of evidence appears to incriminate the drug.

DISCUSSION

Following Duroziez' initial report,¹ the role of digitalis in the production of delirium became the subject of controversy, but in 1950 King² presented convincing evidence that digitalis itself can indeed induce it. Since this time, although reports of digitalis intoxication have been numerous, little mention has been made of delirium. One unusual case was recently described⁵ in which intoxication with digitalis leaf led to prolonged anorexia, nausea, and vomiting which in turn produced vitamin B₁ deficiency; delirium was part of the picture of the resulting Wernicke's encephalopathy. There has been mention of acute psychosis⁹ and disorientation⁷⁻⁹ in other reports of digitalis intoxication, but details of their occurrence are not given and the possible role of other factors is not clearly defined.

Our cases illustrate several clinical points previously noted by other observers, namely, the frequent association of the delirium with aortic valve lesions;¹⁻³ the commoner occurrence in older age groups;¹⁰ variation in the type of psychosis with the personality of the patient;¹ its occasional occurrence as the earliest and possibly the only sign of intoxication^{11, 12} and its occurrence in the absence of electrolyte changes, sedatives, Cheyne-Stokes respiration, and anoxia.³ Case 3 illustrates a point made by Duroziez,¹ that when delirium complicates an already complex syndrome, the drug is not suspected. But for the appearance of bigeminy in this patient, the outcome would almost certainly have been fatal.

There are other features of the present series that are unusual and have not previously received emphasis. Case 1 is of interest because the pattern of previous and subsequent intoxications in the same patient were observed and compared. Delirium characterized only the intoxication here reported in detail. This striking variation in the manifestations of toxicity could not be accounted for by variation in the state of heart failure or electrolyte balance, the degree or rate of intoxication, or the preparation used. This patient was intoxicated on 2 previous occasions with-

in 3 weeks of his toxic delirium and subsequently after an interval of 9 months, and on none of these occasions was delirium produced. On the other hand, King^{2, 3} was able to reproduce the delirium state after a 2- to 3-day period of mental clarity in one case and in another delirium reappeared 2 to 3 weeks after resumption of the digitalis preparation on a lower dosage schedule.

Rapidly excreted glycosides owe their reputation partly to the speed with which toxicity disappears; case 2, therefore, is of particular interest, since the psychotic state outlasted the other manifestations of digoxin intoxication and continued for at least 2 weeks. A similar persistence of arrhythmia from digoxin¹³ and of blindness from digoxin and lanatoside-C¹⁴ has been reported. Finally, neither digoxin nor gitalin seems to have been clearly incriminated as an agent of delirium in previous reports.

SUMMARY

The use and suitability of the term digitalis delirium are briefly discussed. Attention is drawn to the paucity of detailed reports on this important manifestation of digitalis poisoning.

Three cases of digitalis delirium resulting from toxicity with 3 different preparations—gitalin, digoxin, and digitoxin—are presented. The first case demonstrates how the signs of early intoxication in a single patient may vary with different preparations and indeed with the same glycoside on separate occasions. The second case provides an alarming example of delirium which, although provoked by a short-acting glycoside, nevertheless lasted longer than 2 weeks. The third illustrates how easily the diagnosis of digitalis intoxication can go unrecognized when superimposed on a complex clinical picture.

The clinical features of these cases are discussed in the light of previous reports.

SUMMARIO IN INTERLINGUA

Le uso e le proprietate del termino "delirio per digitalis" es discutate brevemente. Es signalate le paucitate de reportos in detalio

relative a iste importante manifestation de invenenamento per digitalis.

Es presentate tres casos de delirio per digitalis, resultante ab toxicitate inducite per tres differente preparatos, i.e. gitalina, digoxina, e digitoxina. Le prime caso illustra como le signos de intoxication precoce in un sol patiente pote variar con differente preparatos e de facto, con le mesme glycosido administrate a differente tempores. Le secunde caso presenta un alarmante exemplo de delirio que durava plus que duo septimanas ben que illo habeva essite provocate per un glycosido a action non prolongate. Le tertie caso demonstra quanto facilmente le diagnose de intoxication per digitalis pote escappar al detection quando iste condition se superimpone a un complexe tableau clinic.

Le aspectos clinic de iste casos es discutate in le lumine de previe reportos.

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These things being prov'd, I think it will appear that it doth go round, is returned, thrust forward, and comes back from the heart into the extremities, and from thence into the heart again, and so makes as it were a circular motion.—WILLIAM HARVEY. *De Motu Cordis*, 1628.

Congenital Insufficiency of the Pulmonary Valve

Including a Case of Fetal Cardiac Failure

By RICHARD D. SMITH, M.D., JAMES W. DUSHANE, M.D., AND
JESSE E. EDWARDS, M.D.

Congenital insufficiency of the pulmonary valve may result if the valvular cusps develop faultily or fail to develop. It is commonly associated with ventricular septal defect, with or without pulmonary stenosis. Under these conditions a continuous precordial murmur may be present. Less commonly, congenital pulmonary valvular insufficiency may appear as an isolated cardiac malformation.

ON A congenital basis, incompetence of the pulmonary valve exists rarely. In some instances there is true absence of the pulmonary valve, while in others regurgitation results from defective formation of the cusps.

Two cases of congenital insufficiency of the pulmonary valve are reported here. In one case wherein no pulmonary valvular tissue was present, the entity was associated with the tetralogy of Fallot. The second case, a newborn infant with anasarca, had contracted pulmonary valvular tissue as an isolated cardiac anomaly. We were able to find in the literature reports of 10 cases of insufficiency of the pulmonary valve.

CASE REPORTS

Case 1

A 4½-year-old boy was seen at the Mayo Clinic in February 1957 for evaluation of congenital heart disease. The birth and development had been normal. It was reported that a heart murmur had first been noted as an aberration in the fetal heart sounds. It was said that cyanosis had been present only on crying during infancy. The patient had had 3 episodes of tachycardia and 3 episodes of heart failure. At each episode of failure he had responded well to digitalization. He had had frequent respiratory infections. Although he frequently stopped to squat when running, no cya-

nosis had been observed at such times. He had been able to keep up with his mates except that he tired more easily and rested more.

The physical examination showed the patient was 41 inches tall and weighed 35 pounds. The brachial blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. The pulse was of bounding type, at a rate of 120 per minute. The color and bodily development were normal. A few crackling rales were heard in both lung bases posteriorly. The precordium was hyperkinetic and bulging. A continuous thrill was palpable at the left third intercostal space. A continuous murmur was audible over the entire precordium, maximally in the left third intercostal space. No distinct second sound was heard over the base of the heart.

The results of laboratory tests of the blood and urine were normal. The thoracic roentgenogram (fig. 1) showed marked cardiac enlargement, with a cardiothoracic ratio of 13 to 18 cm. The shadow of the pulmonary artery was markedly dilated, measuring 4 cm. across. The hilar vascular markings were slightly prominent, the peripheral lung fields normal. The electrocardiogram (fig. 2) showed evidence of right ventricular dilatation, increased pressure in the right ventricle, and right bundle-branch block. Ear oximetry revealed the systemic arterial blood to be 94 per cent saturated with oxygen both at rest and on standing. The saturation fell to 91 per cent during exercise.

The data obtained at cardiac catheterization supplemented by indicator-dilution curves* indicated the presence of a ventricular septal defect and mild pulmonary stenosis. The major shunt was in a left-to-right direction, but was associated with a minor right-to-left shunt. A synopsis of the pressure and saturation data is in table 1. The pulmonary blood flow was 6.1 L. per minute and the systemic blood flow was 2.6 L. per minute. The

*We are indebted to Dr. Earl H. Wood for the physiologic data.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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FIG. 1. Case 1. Posteroanterior roentgenogram of thorax. Cardiac enlargement, prominence of basal shadow and of pulmonary arterial branches.

pulmonary arterial resistance was 460 dynes sec. cm^{-5} and the systemic resistance was 2,660.

The findings established the patient as a candidate for corrective operation with the aid of extracorporeal circulation. At operation the pulmonary trunk and left pulmonary artery were seen to be markedly dilated, and the right pulmonary artery was moderately dilated. Both the right and the left ventricles were enlarged. A ventricular septal defect measuring 1.5 by 1.3 cm. was closed by direct suture. Moderate infundibular pulmonary stenosis was treated by resection of tissue. Regurgitation from the pulmonary artery was noted as of marked degree.

Postoperatively atrioventricular dissociation was persistent and did not respond to treatment. The patient died suddenly 12 days after operation.

Pathologic Features. The heart showed evidence of having been the subject of extracorporeal surgery with right ventriculotomy (fig. 3a). The right ventricular wall was hypertrophied, and its chamber was dilated, being about twice as large as the left ventricular chamber, which was of normal size. The excision of muscle in the infundibular region of the right ventricle had left a free channel between the right ventricle and the pulmonary trunk, and the direct suturing had closed the ventricular septal defect.

At the expected location of the pulmonary valve, no valvular tissue was recognizable (fig. 3b). Instead, at this site was a mild constriction between the right ventricular infundibulum and the origin of the pulmonary trunk. The pulmonary trunk and the major pulmonary arteries were uniformly wider than usual. In the lining of the bifurcation

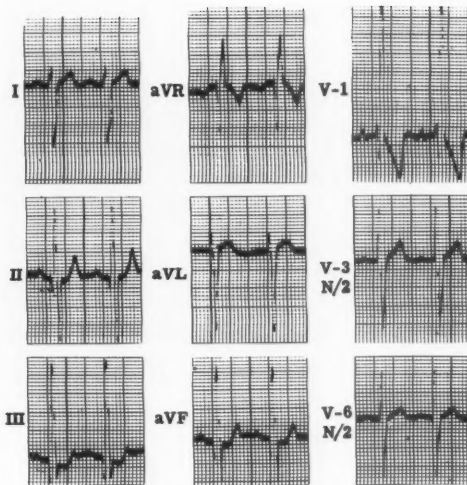


FIG. 2. Case 1. Electrocardiogram.

of the pulmonary trunk was a rough area interpreted as a jet lesion caused by a jetlike stream from the site of the pulmonary stenosis.

The foramen ovale showed a valvular-competent type of patency. The venous connections with the heart were normal. The ductus arteriosus was closed, and the aortic arch was in a normal position. The mitral, tricuspid, and aortic valves were normal.

Histologic examination of the origin of the pulmonary trunk from the right ventricle revealed a bulging into the lumen at the junction of the 2 structures. Loose connective tissue lay in the endocardium at the junction of the vessel and ventricle, but no identifiable valvular tissue was present (fig. 3c).

The pattern of the elastic tissue of the pulmonary trunk was similar to that of the elastic from the aorta. The intrapulmonary arteries and arterioles showed mild degrees of medial hypertrophy.

Case 2

A premature male infant was born November 3, 1958. Fetal hydrops, grade 3, and a meningo-encephalocele were noted at delivery and the heart beat was irregular. The infant died 30 minutes after birth.

The necropsy, in addition to substantiating the clinical observations of fetal hydrops and meningo-encephalocele, disclosed a malformation of the pulmonary valve.

The pulmonary valvular tissue was represented by irregular leaflets too short to close the orifice. Adhesion between the valvular tissues precluded the appearance of distinct commissures (fig. 4).



FIG. 3. Case 1. Pathologic features. *a*. Interior of right ventricle. There is evidence of direct suture of ventricular septal defect and of resection of infundibular tissue. Origin of pulmonary trunk lies above. No valvular tissue is evident. *b*. Pulmonary trunk and aorta viewed from above, pulmonary trunk lying superior to aorta in photograph. As one looks in toward right ventricle from pulmonary trunk, no valvular tissue is identifiable, although mild constriction is present at expected location of valve. *c*. Longitudinal section through origin of pulmonary trunk from right ventricle (lumen was toward left). Slight constriction in gross specimen at junction of pulmonary trunk and right ventricle is evident histologically as convexity on luminal side. Lower part of this same bulge is right ventricular endocardium, thickened by nonspecific connective tissue. No valvular tissue is identifiable. (Elastic-tissue stain; $\times 2$.)

The pulmonary trunk was considerably wider than the aorta, and its wall was thickened. The ductus arteriosus was patent. The foramen ovale also was patent. The right ventricular chamber was of normal size.

Histologic examination of the pulmonary valve revealed it to be composed of loose, young, avas-

TABLE 1.—Blood Pressure and Oxygen Saturation, Case 1

Site of catheter	Pressure (systolic/diastolic) (mm. Hg)	Oxygen saturation (%)
Inferior vena cava	6/2	72
Right ventricle	75/2	85
Mid-right ventricle	87/10	88
Right ventricle at tricuspid valve	86/7	84
Right atrium	8/4	74
Right pulmonary artery	44/33	87
Right pulmonary artery wedge (mean 16)	26/3	94
Femoral artery	125/60	94

cular connective tissue without any distinctive features (fig. 5*a* and *b*).

The adventitia of the pulmonary trunk was thickened with fibrous tissue (fig. 5*c*). Its media had parallel layers of elastic tissue, and in the initial quarter of the media were clear basophilic collections interpreted as "cystic medial necrosis" (fig. 5*d*). The appearance of the muscular arteries and the arterioles of the lung was not remarkable for a newborn infant. Prominent cuboidal cells lined the air spaces. The aortic media showed cystic changes similar to those in the pulmonary trunk.

DISCUSSION

Reports of Others. Of the 10 cases of congenital insufficiency of the pulmonary valve we have found reported in the literature, 2 had been studied clinically, 1 at operation, and 7 at necropsy.

In 1954 Lavenne and associates¹ reported the case of a 46-year-old man who had had episodes of tachycardia with arrhythmia for 26 years and episodes of tachycardia with cyanosis and edema for 1 year. Loud systolic and diastolic murmurs were noted. The patient died suddenly after suffering right-sided hemiplegia and severe lumbar pain. At necropsy the heart was found to be enlarged, with dilatation of the right atrium and hypertrophy of the right and left ventricles. A ventricular septal defect and overriding of the aorta were reported. Pulmonary valvula leaflets as such were not present; in their place were 2 folds of tissue, one above the other. The proximal fold was small and ran

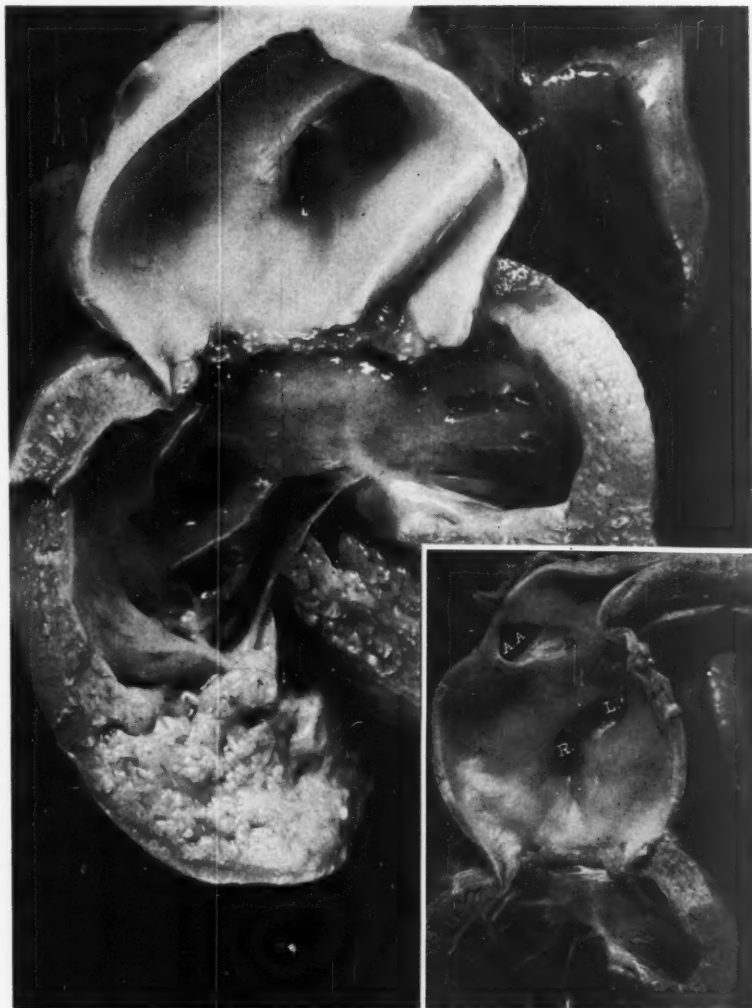


FIG. 4. Case 2. Right ventricle, pulmonary trunk, and great vessels. Insert shows pulmonary trunk arising from right ventricle. Patent ductus arteriosus (*D.*) leads into descending aorta (*T.A.*) just beyond aortic arch (*A.A.*). Origins of right (*R.*) and left (*L.*) pulmonary arteries from pulmonary trunk are shown. Main portion of photograph shows in greater detail the nature of the pulmonary valvular tissue. This is composed of short leaflets that adhere to each other, precluding existence of clearly identifiable commissures.

around the entire circumference of the pulmonary artery. The distal fold lay 2 cm. from the proximal fold and was present only on the posterior third of the circumference of the pulmonary trunk. The pulmonary arteries showed numerous atheromatous plaques, fibrosis of the intimal and muscular layers, and

"onion skin" lesions of the arterioles. A recent renal infarct explained the lumbar pain.

In 1955 Ehrenhaft² reported the case of a 14-year-old boy with a history of decreased exercise tolerance and shortness of breath from 4 years of age. The patient had a markedly enlarged heart with right ventricular



FIG. 5. Case 2. *a.* Longitudinal section through right ventricle and origin of pulmonary trunk, showing shortness of pulmonary valvular tissue. Apparent irregularity of wall of pulmonary trunk is due to peculiarities in plane of section. (Elastic-tissue stain; $\times 30$.) *b.* Greater detail of pulmonary valvular leaflet, which is composed of loose, avascular, nonspecific connective tissue (elastic-tissue stain; $\times 65$). *c.* Pulmonary trunk. Adventitia (at left) is thickened with nonspecific fibrous tissue. Media contains longitudinally oriented elastic fibers and indications of cystic change are visible in its inner portion. (Elastic-tissue stain; $\times 40$.) *d.* Intima and subjacent portions of media of pulmonary trunk, with cystic changes evident in media (hematoxylin and eosin; $\times 200$).

overactivity, loud systolic and diastolic murmurs, and absence of the pulmonary second sound. Roentgenograms and angiocardiograms demonstrated aneurysmal dilatation of the pulmonary artery and right ventricular hy-

pertrophy. The electrocardiogram showed partial right bundle-branch block and right ventricular hypertrophy. On direct visualization of the region of the pulmonary valve during operation no pulmonary valvular

fllets could be identified. The author considered that the pulmonary valve had been "destroyed," implying that the lesion was acquired. It is probable, however, that this is another example of congenital absence of the pulmonary valve.

In 1957 Campeau and associates³ reported the case of a 32-year-old man with a ventricular septal defect, a single coronary artery, and congenital absence of the pulmonary valve. This patient had developed poorly but had not been incapacitated until the onset of congestive heart failure and cyanosis 2 years before death. Systolic and diastolic heart murmurs were heard. Cardiac catheterization 1 year before death established the pressure in the pulmonary artery as 180 systolic and 23 to 28 diastolic, and that in the right ventricle as 180 systolic and 0 diastolic. There was also arterialization of the blood in the right ventricle. The patient died suddenly. At necropsy acute myocardial infarction and hypoplasia of the left coronary artery were found. No pulmonary valvular cusps were identifiable as such; they seemed to be represented by a small fibrous band.

In 1958 Onesti and Harned⁴ reported the case of a 9-week-old male infant with a ventricular septal defect and congenital absence of the pulmonary valve. Congestive heart failure had developed at 3 weeks of age. Systolic and diastolic heart murmurs were heard, and the right pulmonary artery was markedly dilated. Necropsy disclosed that the pulmonary valvular cusps were represented by small, irregular thickenings of fibrous tissue. A large ventricular septal defect was present, and the foramen ovale was patent as well.

Recently Miller, White, and Lev⁵ reported clinical observations of 6 children, each of whom had moderate cyanosis, a "to-and-fro" heart murmur, aneurysmal dilatation of the pulmonary artery, infundibular stenosis, and a bidirectional ventricular shunt. In 4 cases death occurred and necropsy was performed. In each of these 4, infundibular pulmonary stenosis, ventricular septal defect, overriding aorta, and absence of the pulmonary valvular tissue were recorded.

Congenital Basis of Entity. The early reports of absence of pulmonary valvular tissue were concerned with instances studied in older patients. In those cases the assumption that the absence was congenital rather than acquired was based on the absence of evidence in the history to suggest acquirement, the absence of histologic evidence of inflammation or destruction of tissue, and the extreme rarity of any acquired lesions of the pulmonary valve.^{1, 3} With the more recent reports of Onesti and Harned⁴ and Miller, White, and Lev,⁵ and our own case of the newborn infant, the view that deformity of the pulmonary valve which allows pulmonary regurgitation represents a congenital malformation seems well established.

Associated Conditions and Signs. Absence of the pulmonary valve usually occurs in association with ventricular septal defect, with or without pulmonary stenosis. It was a single cardiac anomaly, however, in the surgical case of Ehrenhaft and in our case 2.

According to Miller,⁶ the combination of tetralogy of Fallot with the murmur of pulmonary insufficiency suggests absence of the pulmonary valve. The several reports cited indicate that prominent dilatation of the major pulmonary arteries is common in congenital insufficiency of the pulmonary valve, and our cases bear this out.

Significance of Fetal Hemodynamics. In our case 2 the anasarca found at necropsy is attributed to cardiac failure, which in turn is attributed to fetal pulmonary valvular insufficiency. It is to be emphasized that the dynamics of this valvular dysfunction in the fetus is different from that in postnatal life. Experimental evidence^{7, 8} indicates that creating pulmonary valvular insufficiency in the postnatal state causes little if any recognizable effect. This is explained by the low pulmonary pressure in postnatal life. In the fetus, on the other hand, pulmonary pressures are at the same levels as systemic pressures. In the presence of pulmonary valvular incompetence the high fetal pulmonary arterial pressure would serve to cause regurgitant flow across the pulmonary valve during ven-

tricular diastole. Of additional significance is the free communication of the systemic and pulmonary arterial systems through the ductus arteriosus during fetal life. Thus when pulmonary regurgitation occurs in fetal life it is possible for aortic blood to run off into the pulmonary arteries and so into the right ventricle. The peculiarities of the fetal circulation are such that in fetal life pulmonary valvular insufficiency may cause a peculiar form of aortic run-off resembling that which occurs in aortic valvular insufficiency.

Cardiac failure during fetal life, which is rare, most often is caused by premature closure of the foramen ovale. Our case 2 indicates that pulmonary valvular incompetence is to be added to those uncommon conditions that can be responsible for fetal cardiac failure.

Certain Etiologic Speculations. The significance of the "cystic medial necrosis" that was observed in the aorta and pulmonary trunk of our second case is difficult to evaluate. It is interesting to speculate, though it cannot be proved, that this was a manifestation of arachnodaetly. Another matter for speculation is whether dilatation of the pulmonary trunk, resulting from the medial change, may have created stresses on the developing pulmonary valvular tissue and in this way caused the deformity of the cusps.

SUMMARY

Congenital insufficiency of the pulmonary valve, a rare anomaly, is caused by either absence or deformity of valvular tissue.

More commonly the condition is associated with a ventricular septal defect with or without pulmonary stenosis. In this association a continuous precordial murmur may be a prominent clinical sign, as in 1 of the 2 cases here reported.

Less commonly, incompetence of the pulmonary valve occurs as an isolated condition. In the second of the 2 cases here reported, this was associated with deformity of valvular tissue and with cardiac failure during fetal life.

SUMMARY IN INTERLINGUA

Congenite insufficientia del valvula pulmonar es rar. Illo es un anomalia causate per le absentia o per le deformitate del histos valvular.

Le condition occurre plus communmente in association con un defecto ventriculo-septal con o sin stenosis pulmonar. In iste association un continue murmure precordial es frequentemente un prominente signo clinic, como il esseva le caso in 1 del 2 patientes hic desribite.

Incompetentia del valvula pulmonar occurre minus frequentemente como condition isolate. In le secunde caso hic presentat e, le anormalitate in question esseva associate con deformitate del histos valvular e con disfallimento cardiac durante le vita fetal.

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Detection of Pulmonic and Tricuspid Valvular Regurgitation by Means of Indicator Solutions

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AND ANDREW G. MORROW, M.D.

The presence of pulmonic and tricuspid valvular regurgitation may often be suspected from careful clinical examination. However, the validity of the generally accepted clinical criteria remain to be established by techniques that permit the direct demonstration of reverse flow across these valves during life. This has been made possible by the detection of cardiogreen and of radioactive krypton (Kr^{85}) in the right atrium or right ventricle after injection of these substances into a distal chamber.

ALTHOUGH the presence of valvular regurgitation may be suspected from clinical studies, the actual demonstration of blood traversing a valve in reverse direction is necessary for a definitive diagnosis. Indicator-dilution curves recorded from a systemic artery following injections into the right side of the heart are often modified by the presence of a regurgitant valve between the sites of injection and of sampling.¹⁻³ Decreased cardiac output or a left-to-right shunt may, however, obscure the changes produced in such curves by valvular regurgitation.

Mitral regurgitation has been demonstrated by the prompt appearance in the left atrium of either an indicator dye^{4, 5} or of a radiopaque medium⁶ following injection into the left ventricle. In the presence of aortic regurgitation, indicator dye injected into the descending thoracic aorta regurgitates to the ascending aorta and may be detected in the right ear.⁷ This lesion may also be demonstrated by thoracic aortography.⁸ The reflux of radiopaque dye into the right ventricle following its injection into the pulmonary artery has recently been observed in the presence of pulmonic regurgitation.⁹

It is the purpose of this report to describe techniques for the detection of pulmonic and tricuspid valvular regurgitation that may be applied conveniently at the time of right

heart catheterization, and to present the results obtained in 29 patients studied at the National Heart Institute. A similar approach to diagnosis has also been described recently by Bajec, Birkhead, Carter, and Wood.¹⁰

METHODS

Right heart catheterization was performed with a no.-9 double-lumen Cournand catheter, modified so that the openings of the 2 lumina were 5 cm. apart. When the competency of the pulmonic valve was studied, the catheter was positioned so that the distal opening was in the pulmonary artery and the proximal one in the right ventricle. When tricuspid valve function was examined, the distal lumen opened into the right ventricle, while the proximal opened into the right atrium. Simultaneous pressures were recorded from each chamber immediately prior to and following injection of the indicator in order to confirm the position of the catheter.

Cardiogreen (tricarboeyanine) dye¹¹ was injected through the distal opening of the catheter as blood was sampled continuously from the proximal opening (fig. 1). The concentration of the indicator was determined by withdrawal through a cuvette densitometer¹² by means of a constant-rate motor-driven syringe. Time-concentration curves were recorded either with a photographic cathode-ray instrument or a direct-writing recorder.

The order of magnitude of the relationship between regurgitant and forward flows was estimated by the "forward triangle" method described by Hetzel and collaborators.^{13, 14} The "regurgitant fraction" was calculated as the ratio of the product of the build-up time and peak-concentration of the "regurgitant curve" to that of the "recirculation curve" (fig. 2). It is realized that this ratio does not provide precise quantification.

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*Manufactured by Nuclear Corporation of America, Brooklyn, N. Y.

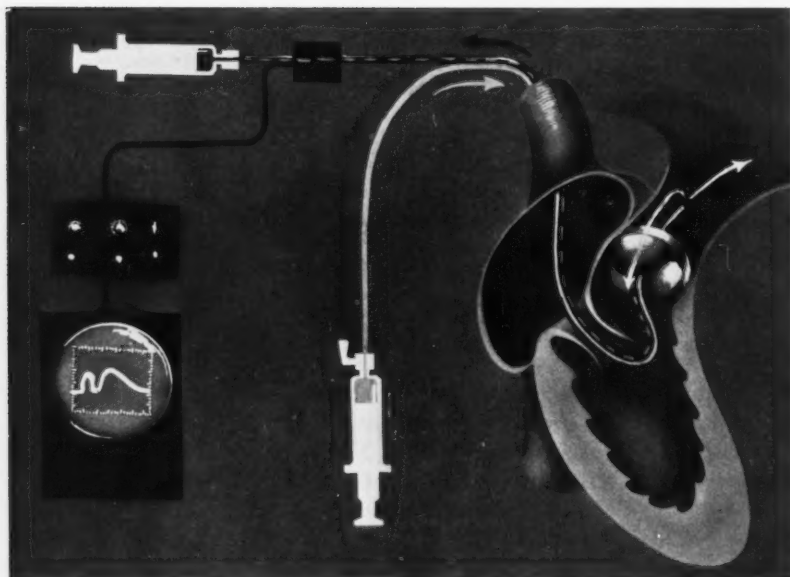


FIG. 1. Representation of the test for competency of the pulmonic valve with cardiogreen dye. Dye is injected through the distal opening of the catheter, and regurgitates back into the right ventricle. It is detected by sampling right ventricular blood from the proximal opening of the catheter through a cuvette densitometer.

In 12 of the 29 patients valvular competency was studied in a similar manner with injections of 30 to 50 μ c. of radioactive krypton (Kr^{85}) solution into the distal opening of the catheter. Immediately after injection blood was sampled at a constant rate for 10 seconds from the proximal lumen and for 15 seconds from a systemic artery. The radioactivity in these samples was then measured by inserting them into a continuous gas-flow Geiger-Muller tube.⁶

RESULTS

In the presence of a competent valve, either no dye or only a minimal quantity appeared in the proximal chamber immediately after injection. Fifteen to 20 seconds after injection, dye that had recirculated through the systemic circuit appeared (figs. 3 and 4). When valvular regurgitation was present, a substantial amount of dye appeared in the proximal chamber within 2 seconds of the onset of the injection, well before the appearance of the recirculation curve (figs. 2 and 5). In the presence of valvular regurgitation combined with a left-to-right shunt entering upstream to the proximal catheter opening, the

curve produced by the regurgitant valvular flow was inscribed significantly earlier than the curve produced by the shunted blood; the latter, while delayed in its path through the pulmonary circulation and to the right side of the heart, nevertheless appeared earlier than the systemic recirculation curve (fig. 6).

The competency of the pulmonic valve was examined in 28 patients, and in 7 of these significant regurgitation was considered to be present with "regurgitant fractions" ranging from 17 to 72 per cent. Three of these 7 patients (W.J., J.B., J.S.) had previously had portions of their pulmonic valves excised at the time of pulmonary valvulotomy, but only 2 (J.B., J.S.) had murmurs considered typical of pulmonic regurgitation. Another patient (M.B.) had previously undergone pulmonic valvulotomy and closure of a small ventricular septal defect in which no valvular tissue was removed. A murmur typical of pulmonic regurgitation developed. One patient (C.C.) had mitral regurgitation, pulmonary hypertension, and a typical Graham Steell murmur.

Patient J.K., who had not been operated upon, had the murmurs considered typical of pulmonic stenosis and regurgitation. At right heart catheterization, there was a gradient of 5 mm. Hg across the pulmonary valve, and the diastolic pressures in the pulmonary artery and right ventricle were identical. The seventh patient (S.C.) had an atrial septal defect, pulmonary hypertension, and a typical Graham Steell murmur; the presence of pulmonic regurgitation was confirmed at the time of operative closure of the defect when a distinct jet of blood was felt in the right ventricle during diastole. In only 3 (W.J., J.K., M.B.) of these 7 patients was the end-diastolic pressure in the pulmonary artery identical to that in the right ventricle. Pulmonary regurgitation was not suspected in 5 other patients who had "regurgitant fractions" ranging from 2 to 6 per cent. It is believed that such minute amounts of reflux do not necessarily indicate organic valvular dysfunction, but are presumably artifacts produced by the presence of the catheter. There was no relation between the presence of this small degree of regurgitation and the pulmonary artery pressure.

The competency of the tricuspid valve was tested in 17 patients and in 8 of these significant regurgitant flow was demonstrated. The "regurgitant fractions" ranged from 11 to 65 per cent in 7 of the patients and could not be calculated in the eighth, a patient with a very prolonged circulation time in whom no recirculation curve had appeared after 55 seconds of sampling. In all 8 of these patients there was clinical evidence of tricuspid regurgitation and the right ventricular pressure was elevated (table 1); in 5 of these, the mean right atrial pressure and the right atrial "v" wave pressures were elevated. In 2 of the patients with significant tricuspid regurgitation the diagnosis was confirmed at subsequent postmortem examination. In one of these patients, J.O., the tricuspid ring was widely dilated and the valve leaflets were held in a position of partial inversion into the right ventricle. In the other patient, A.R., the tricuspid valve was both stenotic and regurgi-

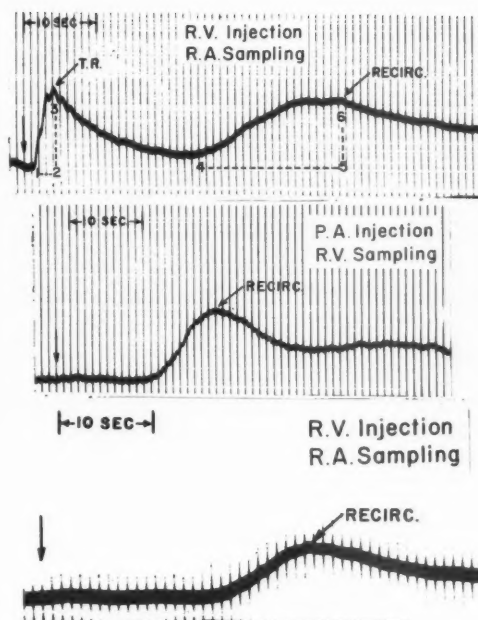


FIG. 2 Top. Indicator-dilution curve obtained after right ventricular injection and right atrial sampling in a patient with rheumatic heart disease, mitral stenosis and regurgitation and tricuspid regurgitation. Vertical arrow, time of injection. The first upward deflection (T.R.) represents the dye that regurgitated across the tricuspid valve. The systemic recirculation curve is seen on the right (RECIRC.). 1-2, build-up time; 2-3, peak concentration of the regurgitant curve; 4-5, build-up time; 5-6, the peak concentration of the recirculation curve. Tricuspid regurgitation was also revealed with the Kr⁵⁵ test performed on this patient.

FIG. 3 Middle. Dye-dilution curve resulting from pulmonary artery injection and right ventricular sampling in patient L.R. with rheumatic heart disease, mitral stenosis, and aortic insufficiency. The absence of dye in right ventricular blood prior to recirculation is thought to exclude pulmonic regurgitation. The Kr⁵⁵ test also showed the absence of pulmonic regurgitation.

FIG. 4 Bottom. Dye-dilution curve after right ventricular injection and right atrial sampling in a patient without tricuspid regurgitation.

tant, rigid and immobile with a fixed opening 1.5 cm. in diameter. Patient S.C. had an atrial septal defect with pulmonary and right ventricular systolic hypertension. The tricuspid regurgitant fraction was 11 per cent and a small regurgitant jet was palpable at opera-

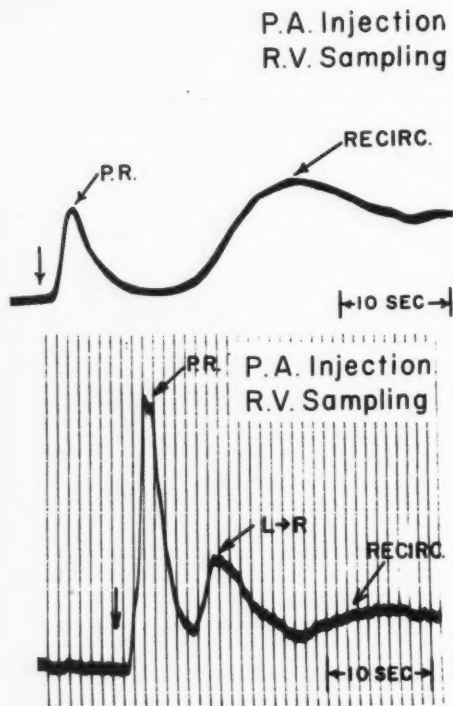


FIG. 5 *Top.* Dye-dilution curve obtained from the right ventricle following pulmonary artery injection in a patient with pulmonary regurgitation. The dye that appears immediately (*P.R.*) indicates pulmonic reflux and precedes the recirculation curve (*RECIRC.*).

FIG. 6 *Bottom.* Dilution curve resulting from pulmonary artery injection and right ventricular sampling in a patient who had a portion of his pulmonic valve excised at the time of pulmonary valvotomy for pulmonic stenosis. A left-to-right shunt due to an atrial septal defect persisted. The first component of the curve (*P.R.*) is indicative of pulmonic regurgitation, the second (*L→R*) is related to blood that has been shunted across the atrial septal defect, and the third component (*RECIRC.*) is due to systemic recirculation.

tion. In only one instance minimal ("catheter induced") tricuspid regurgitation was encountered with regurgitant fraction of 3 per cent.

It has been demonstrated previously that approximately 95 per cent of Kr^{85} injected into the venous system or right side of the heart is eliminated into the expired air during its passage through the pulmonary circulation.¹⁵⁻¹⁸ The small remaining fraction that

reaches the systemic arterial bed does not behave in a fashion similar to a simple intravascular indicator such as cardiogreen. A portion leaves the intravascular compartment and diffuses into the interstitial fluid as well as into the cells,¹⁹ further diminishing the quantity of Kr^{85} in the systemic venous blood immediately after injection into the right side of the heart or pulmonary artery. The presence of Kr^{85} in the blood sampled from the right atrium or right ventricle immediately after injection into the right ventricle or pulmonary artery could therefore result only from valvular regurgitation.

Twelve patients had both Kr^{85} and cardiogreen dye tests for pulmonic regurgitation while 5 had both tests for tricuspid regurgitation. The results were in general agreement. In 8 tests the cardiogreen "regurgitant fraction" exceeded 15 per cent and the right heart Kr^{85} count per minute (c.p.m.) exceeded background by more than 100 c.p.m. Similarly, in 7 tests the cardiogreen regurgitant fraction ranged between 0 and 3 per cent while the right heart Kr^{85} activity ranged between 0 and 54 c.p.m. above background. However, the results in the other 2 patients indicated a discrepancy between the 2 tests. In patient J.B., significant pulmonic regurgitation was revealed only by cardiogreen dye while in patient M.E., it was demonstrated only with Kr^{85} .

DISCUSSION

The techniques for the detection of pulmonic and tricuspid valvular regurgitation described herein have been found simple and convenient to apply at the time of right heart catheterization and should prove of considerable clinical value. The diagnosis of pulmonary regurgitation is usually made when a patient with evidence of pulmonary hypertension presents with a high-pitched, decrescendo, blowing diastolic murmur along the left sternal border, unaccompanied by the peripheral dynamics of aortic regurgitation. Seven such patients were studied with an indicator-dilution method for the detection and estimation of aortic regurgitant flow.⁷ It was with considerable surprise that mild aortic

TABLE 1.—Results of Dye-Dilution Tests for Valvular Regurgitation

	Pressure		RA		Regurgitant fraction		Diagnosis
	PA S/D	RV S/D	Mean	V Wave	Tricuspid	Pulmonic	
I. P.	27/11	28/1	4	6	—	0	ASD
L. J.	22/7	22/4	3	6	—	0	ASD
M. S.	42/20	42/8	7	10	—	0	MS, MI
A. L.	29/10	33/1	2	3	—	0	PDA
D. D.	54/12	54/0	1	3	0	0	VSD
M. B.	34/14	35/4	5	8	—	0	MS, AI
P. D.	47/34	48/4	5	7	—	0	VSD
A. R.	80/40	80/10	10	14	57	0	MS, MI, TS, TI
M. P.	72/34	73/7	8	18	50	0	MS, MI, TI
F. L.	25/9	28/5	5	6	—	0	AS
L. M.	40/20	43/4	4	7	65	3	MS, MI, TI
R. P.	41/23	42/0	5	6	0	2	MS, AI, TS
W. J.	20/3	45/3	4	6	0	53	PS, PI, ASD (postop.)
J. B.	64/30	66/10	6	7	—	29	PI, Tet. of Fallot (postop.)
C. C.	50/20	50/3	2	4	0	17	MI, PI
H. E.	56/14	58/5	10	16	22	2	MS, MI, TI
S. C.	78/30	80/4	4	3	11	23	ASD, PI, TI
J. S.	15/5	35/0	1	3	3	18	PS, PI (postop.)
C. M.	15/7	16/0	2	3	0	—	MI
C. H.	23/7	23/6	7	8	0	2	AI, MS
J. O.	68/38	70/7	7	11	*	0	MS, MI, AS, AI, TI
R. J.	18/6	16/3	2	3	0	6	ASD
L. R.	50/30	54/4	4	5	—	0	MS, AI
D. M.	22/10	22/10	3	4	—	0	MS, AI
M. E.	40/20	40/6	10	15	12	0	MS, MI, TI
D. W.	73/34	75/7	5	6	59	0	MS, TI
J. K.	22/8	48/8	4	5	—	72	PS, PI
B. S.	43/22	43/5	4	4	0	0	AI, MI
M. B.	28/2	28/2	—	—	—	55	VSD, PS, PI (postop.)

All pressures expressed in mm. Hg: S/D, systolic/diastolic pressures; *large regurgitant curve but no recirculation curve recorded; ASD, atrial septal defect; MS, mitral stenosis; MI, mitral insufficiency; PDA, patent ductus arteriosus; AI, aortic insufficiency; VSD, ventricular septal defect; TI, tricuspid insufficiency; TS, tricuspid stenosis; AS, aortic stenosis; PS, pulmonic stenosis; PI, pulmonic insufficiency.

regurgitation was discovered in 6 of these 7 patients believed on clinical grounds to have pulmonary regurgitation. If the indicator-dilution methods are applied to the study of both the aortic and pulmonic valves, the origin of any diastolic murmur due to regurgitation may be determined. A patient recently studied illustrates the clinical application of these techniques.

L.R. (Clinical Center #00-24-61), an 18-year-old girl, was admitted for diagnostic study and the treatment of rheumatic heart disease. She had had acute rheumatic fever at 8 years of age and was told shortly thereafter that she had a heart murmur. No symp-

toms ensued until 1 year prior to admission when exertional dyspnea, easy fatigability, occasional paroxysmal nocturnal dyspnea, and hemoptysis began. On physical examination the blood pressure was 106/70; the pulse was 94 and regular. The point of maximal impulse was in the left midclavicular line in the fifth left intercostal space and there was only a slight right ventricular lift. At the apex the first heart sound was accentuated. The second heart sound in the pulmonic area was loud and showed normal respiratory splitting. In the pulmonic area and along the left sternal border there was a grade-II high-pitched, decrescendo, blowing diastolic murmur, and

TABLE 2.—Results of Radioactive Krypton Tests for Valvular Regurgitation

Patient	Right ventricular injection		Pulmonary artery injection	
	KR ⁸⁵ counts/min. in RA	Dye-dilution "regurgitant fraction"	KR ⁸⁵ counts/min. in RV	Dye-dilution "regurgitant fraction"
L. R.	—	—	3	0
W. J.	12	0	301	53
H. E.	579	22	44	12
C. H.	—	—	54	2
J. O.	245	*	0	0
L. M.	230	65	31	3
J. B.	—	—	7	29
J. S.	—	—	199	18
S. C.	—	—	245	23
D. M.	—	—	7	0
M. E.	139	59	123	0
M. B.	—	—	230	55

All counts have been corrected for background. RA, right atrium; RV, right ventricle; *, very large regurgitant curve, but no recirculation curve recorded.

a grade-II rumbling diastolic murmur with presystolic accentuation was heard at the apex. The electrocardiogram showed right ventricular hypertrophy and right axis deviation. X-rays revealed the heart to be slightly enlarged in its transverse diameter and there was prominence of the main pulmonary artery segment and enlargement of the left atrium. Right heart catheterization revealed the pulmonary artery pressure to be 50/30, the cardiac index was 1.98 L./min./M², and no shunts were present. Transbronchial left heart catheterization revealed a mean left atrial pressure of 22 mm. Hg and the end-diastolic gradient across the mitral valve was 20 mm. Hg. It was considered that this patient had mitral stenosis and that the diastolic murmur along the left sternal border represented pulmonic regurgitation. However, no regurgitation was demonstrated either by the dye-dilution method (table 1, fig. 3) or by the Kr⁸⁵ technic (table 2). Retrograde aortic catheterization and quantification of aortic regurgitation was then carried out and revealed regurgitation of dye from the thoracic aorta at the level of the eighth thoracic vertebra to the origin of the innominate artery.

The final diagnosis was severe mitral stenosis and moderate aortic regurgitation.

In the past, the definitive diagnosis of tricuspid regurgitation has rested primarily on clinicopathologic correlations. It was suggested by the contour of the right atrial pressure pulse in 60 patients studied by Sepulveda and Lucas.²⁰ However, tricuspid regurgitation had been suspected clinically in only 23 percent of this group. On the other hand, in the present investigation, substantial tricuspid regurgitation was demonstrated in patients L.M., S.C., and D.W. in whom the right atrial pressure pulse was normal. In this connection it is also of interest that the right atrial pressure pulse was not modified in the 4 patients with congenital left ventriculo-right atrial communications whom we have recently studied.²¹ In this malformation, blood is ejected into the right atrium during ventricular systole in a manner similar to tricuspid regurgitation.

It is anticipated that the methods described herein will provide a more precise approach to the diagnosis of tricuspid regurgitation and make clinico-hemodynamic-pathologic correlations more meaningful than heretofore. The recognition of tricuspid regurgitation may be of considerable clinical importance. It has been pointed out by Schilder and Harvey²² that patients with mitral stenosis and tricuspid regurgitation have been denied commissurotomy because the presence of a loud systolic murmur led to the erroneous diagnosis of mitral regurgitation. Such diagnostic errors should be obviated by the recognition of tricuspid regurgitation with the indicator-dilution or radioactive gas technics.

SUMMARY

Technics for the demonstration of pulmonic and tricuspid regurgitation and the estimation of the magnitude of regurgitant flow are described. The pulmonic valve was studied by positioning a modified double-lumen catheter so that the distal lumen opened into the pulmonary artery and the proximal lumen opened into the right ventricle. When tricuspid function was examined, the distal lumen

opened into the right ventricle and the proximal one into the right atrium. Cardiogreen dye and radioactive krypton (Kr^{85}) were injected through the distal opening of the catheter and sampled from the proximal opening. With a competent valve, either no dye or Kr^{85} or only a minimal quantity could be detected in the proximal chamber immediately after injection. In the presence of valvular regurgitation, substantial amounts appeared in the proximal chamber immediately after injection. Regurgitation was present in 7 of the 28 patients in whom the pulmonic valve was examined, with regurgitant fractions ranging from 17 to 72 per cent. Tricuspid regurgitation was proved in 8 of the 17 patients studied; the regurgitant fractions were 11 to 65 per cent. The methods described appear reliable, simple to apply in the course of right heart catheterization, and of clinical value in the study of patients with known or suspected valvular heart disease or with heart murmurs of uncertain etiology.

SUMMARY IN INTERLINGUA

Es describe technicas pro le demonstration de regurgitation pulmonie e tricuspid e pro le estimation del magnitudine del fluxu regurgitante. Le valvula pulmonie esseva studiate per positionar un modificate catheter a lumine duple de maniera que le lumine distal communicava con le arteria pulmonar e le lumine proximal con le ventriculo dextere. In le examine del function tricuspid, le catheter esseva positionate de maniera que le lumine distal communicava con le ventriculo dextere e le lumine proximal con le atrio dextere. Un colorante cardio-verde e krypton radioactive (Kr^{85}) esseva injectate via le lumine distal del catheter e specimenes esseva obtenite ab le lumine proximal. Quando le valvula es competente, nulle colorante e nulle Kr^{85} — o al minus solmente un quantitate minimal de illos — poteva esser detegite in le camera proximal immediatamente post le injection. In le presentia de regurgitation valvular, quantitates substantial del indicadores appareva in le camera proximal immediatamente post le injection. Regurgitation esseva presente in 7 del

28 patientes in qui le valvula pulmonie esseva examine. Le fractiones regurgitante variava inter 17 e 72 pro cento. Regurgitation tricuspid esseva constatate in 8 del 17 patientes studiate. Le fractiones regurgitante variava inter 11 e 65 pro cento. Le methodos describe es apparentemente digne de confidentia, simple a applicar in le curso de catheterismo dextero-cardiac, e de valor clinic in le studio de patientes con establite o suspicite morbo de valvula cardiac o con murmures cardiac de etiologia incerte.

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With the invention of the microscope we can mark the first positive step towards the goal to-day. A Jesuit priest, Kircher, in 1671, was the first to investigate putrefying meat, milk, and cheese with the crude microscope of his day, and left us indefinite remarks concerning 'very minute living worms' found therein. Four years after Kircher a Dutch linen merchant, Antonius von Leeuwenhoek, by improving the lenses of the microscope saw in rain-water, putrefying fluids, intestinal contents, and saliva, minute, moving, living particles, which he called 'animaleculae.' In medical circles of his day these observations aroused the keenest interest, and the theory that these 'animaleculae' might be the cause of all disease was eagerly discussed. Plenciz, of Vienna, after much observation of various fluids, putrefying and otherwise, wrote, in 1762, that it was his firm belief that the phenomena of diseases and the decomposition of animal fluids were wholly caused by minute living things.—WILLIAM OSLER. *Aequanimitas and Other Addresses*. Blakiston & Co., Philadelphia, and T. K. Lewis, London, 1904.

Correlation of Heart Rate During Norepinephrine Infusion with Pulse Pressure Following Amyl Nitrite Inhalation

By FRANK A. FINNERTY, JR., M.D., GLORIA DECARLO MASSARO, M.D.,
FREDRICK SIGDA, M.D., AND MARTIN RYAN, M.D.

Conway and Smith have suggested that a decrease in the pulse pressure following inhalation of amyl nitrite might be associated with loss of aortic elasticity. Studies in this laboratory have suggested that a decreased bradycrotic response during infusion of norepinephrine might also be associated with loss of aortic elasticity. It was hoped that further support might be given to such a hypothesis if both procedures gave similar results in the same patients. The present study was designed to compare the effect of inhalation of amyl nitrite on the pulse pressure and infusion of norepinephrine on the heart rate in normal, hypertensive, and arteriosclerotic subjects.

CONWAY and Smith¹ demonstrated a greater decrease in pulse pressure during inhalation of amyl nitrite in patients with arteriosclerotic hypertension than in hypertensive patients without arteriosclerosis or in young normal patients. Studies in this laboratory² have demonstrated a decreased bradycrotic response during infusion of norepinephrine in patients with arteriosclerosis whether the arterial pressure was normal or elevated. Both these groups^{1, 2} have postulated independently that such procedures might be used to assess the elastic qualities of large vessels. Thus a marked bradycrotic response during infusion of norepinephrine and no significant decrease in pulse pressure following inhalation of amyl nitrite would indicate

normal elasticity of large vessels while a decreased bradycrotic response during infusion of norepinephrine or a greater decrease in pulse pressure following amyl nitrite would indicate loss of elasticity of these vessels. It was hoped that further support might be given to such a hypothesis if both procedures gave similar results in the same patients. The present study was designed to compare the effect of inhalation of amyl nitrite on the pulse pressure and infusion of norepinephrine on the heart rate in normal, hypertensive, and arteriosclerotic subjects.

METHODS AND MATERIALS

The patients were from the wards and clinics of the District of Columbia General Hospital. Twenty-five patients were studied; 7 were male and 18 female. Six patients were without any manifest cardiovascular disease (group 1). Six patients demonstrated clinical evidence of arteriosclerosis (see below for explanation) with a normal arterial pressure (group 2), and 13 patients showed evidence of arteriosclerosis with an elevated arterial pressure (group 3).

The average age of the 6 patients without cardiovascular disease (group 1) was 38 (20 to 59) years. The average femoral arterial pressure (systolic plus diastolic divided by 2) was 110 ± 9 mm. Hg. Complete physical examination with particular emphasis on the cardiovascular system was normal. The electrocardiogram, chest roentgenogram, and urinalysis were all normal.

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This investigation was supported by research grants from the American Heart Association; the National Heart Institute (H-2509), U. S. Public Health Service; Ciba Pharmaceuticals, Inc., Summit, N. J.; Charles Pfizer & Company, Inc., Brooklyn, N. J.; Merck Sharp & Dohme, West Point, Pa.; and the Quibb Institute for Medical Research, New Brunswick, N. J.

This work was done during Dr. Finnerty's tenure of an Established Investigatorship of the American Heart Association.

The average age of the 6 patients with arteriosclerosis and normal arterial pressure (group 2) was 70 (58 to 82) years. The average femoral arterial pressure was 115 ± 15 mm. Hg. In no patient was there a history of hypertension. In 2 patients there was a history of cerebral vascular accident. Ophthalmoscopic examination revealed an increase in the arteriolar light reflex and tortuosity and narrowing of the retinal arterioles in 5 patients. Cataracts prevented ophthalmoscopic examination in the remaining patient. There was unilateral absence of the posterior tibial pulsation in 3 patients. The electrocardiogram was normal in 1 patient, demonstrated the pattern of myocardial ischemia in 2 patients, and old anterior myocardial infarction in 2 patients. Chest x-ray revealed an enlarged heart and widened and elongated aorta in 2 patients and a heart of normal size with elongation and dilatation of the aorta in 4 patients. Each patient demonstrated at least 3 of the above findings.

The 13 patients in group 3 had chronic hypertensive vascular disease. Their average age was 56 (32 to 72) years. The average duration of hypertension in these patients was 9 (6 to 17) years. The average femoral arterial pressure was 168 ± 39 mm. Hg. Ophthalmoscopic examination revealed arteriovenous nicking plus tortuosity of the retinal vessels in 11 patients and arteriovenous nicking plus tortuosity plus exudates and hemorrhages in 2 patients. Roentgenograms of the chest revealed enlargement of the heart in the transverse diameter in all patients. The electrocardiogram was normal in 1 patient, showed the pattern of left ventricular hypertrophy and posterior myocardial infarction in 2 patients, and the pattern of left ventricular hypertrophy in 10 patients.

The patients were brought to the laboratory in the fasting state without premedication. Following local infiltration of the skin with 1 per cent procaine a 17-gauge needle was inserted into the femoral artery. The arterial pressure was recorded directly by means of a strain-gage transducer and a direct-writing recorder.

Following attainment of a steady state, norepinephrine bitartrate (Levophed) was administered as an intravenous infusion in a concentration of 4 μ g. per ml. of 5 per cent dextrose in water. The rate of infusion was regulated according to the increase in arterial pressure and the decrease in heart rate and varied between 5 and 14 μ g. per minute. The endpoint of the experiment was taken as a rise of arterial pressure in excess of 25 per cent or a decrease in heart rate of more than 10 beats per minute. In those patients in whom one or the other endpoint was not reached, the norepinephrine infusion was continued for at least 10 minutes.

Following return of the arterial pressure and heart rate to control levels a crushed vial of amyl nitrite was held under the subject's nose. The patient was instructed not to sniff, but to take 2 normal inspirations. The arterial blood pressure was recorded directly throughout the entire procedure until it returned to control levels. In the measurement of the pulse pressure trends, particular care was taken to compare equivalent beats with respect to heart rate and respiration before and after the onset of the depressor effect of amyl nitrite. The experimental pulse pressure observation was noted before the development of tachycardia. The response of the arterial pressure during inhalation of amyl nitrite was tested at least twice in the same patient.

RESULTS

The results are shown in table 1. The greater decrease in pulse pressure following inhalation of amyl nitrite occurred in the same patients who exhibited a decreased bradycerotic response during infusion of norepinephrine. Little or no overlapping occurred between the normal and abnormal responses in both procedures. A decrease of more than 10 beats per minute in heart rate occurred during norepinephrine infusion in every patient who demonstrated less than a 13 per cent reduction in pulse pressure following inhalation of amyl nitrite (groups 1 and 3A) (fig. 1). A reduction in heart rate of no more than 4 beats per minute during norepinephrine occurred in those patients who exhibited more than a 16 per cent reduction in pulse pressure following inhalation of amyl nitrite (groups 2 and 3B) (fig. 1).

DISCUSSION

These responses in pulse pressure and heart rate were not related to the age of the patient, the control level of arterial pressure, or the percentage increase or decrease in arterial pressure. The patients in the arteriosclerotic group with normal arterial pressure (group 2) were older than the patients without cardiovascular disease (group 1). However, the ages of the patients in group 3A in whom normal responses to norepinephrine and amyl nitrite were witnessed were similar to the ages of the patients in group 3B who demonstrated abnormal responses to norepi-

nephrine and amyl nitrite. The previous studies from this laboratory, which have reported a normal bradycrotic response during norepinephrine in elderly subjects without obvious arteriosclerosis, would also tend to minimize the importance of age as the sole cause for the decreased bradycrotic response during infusion of norepinephrine.²

The normal level of arterial pressure in groups 1 and 2 and the elevated arterial pressure in groups 3A and 3B demonstrate the lack of importance of the control level of arterial pressure in determining the heart rate response during norepinephrine and the pulse pressure response following amyl nitrite. Although a greater decrease in the arterial pressure following inhalation of amyl nitrite occurred in those patients who exhibited a greater decrease in pulse pressure, these differences are probably not significant. No correlation exists between the degree of elevation of arterial pressure and the changes in heart rate.

The mechanisms for the different responses of heart rate during norepinephrine and the pulse pressure following amyl nitrite are not known. It may be that the abnormal response to both these agents is in some way related to arteriosclerosis. Previous studies from this laboratory revealed a decreased bradycrotic response during norepinephrine in patients who demonstrated several clinical signs of arteriosclerosis.² Similarly, Conway suggested that one could predict a greater decrease in pulse pressure following amyl nitrite in patients with the arteriosclerotic type of hypertension.² The response of the heart rate during norepinephrine and the pulse pressure following inhalation of amyl nitrite could not be predicted in the hypertensive patients presented here (groups 3A and 3B). The ages of these patients, duration of their hypertension, retinal vascular changes, heart size, width of the aorta, and electrocardiographic findings all were similar.

Heymans and Neil³ have shown that the response of the carotid sinus baroreceptor nerves (and presumably aortic sinus) depends on the distensibility of the carotid sinus. Loss

TABLE 1.—Changes in Arterial Pressure and Heart Rate During Norepinephrine Infusion with Arterial Pressure and Pulse Pressure Following Amyl Nitrite Inhalation

Group	1	2	3A	3B
Number of patients	6	6	5	8
<i>Norepinephrine</i>				
Control arterial pressure (mm. Hg)	110±9	115±15	180±52	160±16
Arterial pressure during infusion (mm. Hg)	139±10	141±19	215±53	190±21
Per cent increase arterial pressure	26±5	23±8	19±7	19±6
Heart rate (beat/min.)	70±8	75±14	74±15	66±15
Heart rate during infusion (beat/min.)	57±7	73±15	60±17	64±16
Per cent decrease heart rate	19±4	3±3	19±8	3±3
<i>Amyl nitrite</i>				
Control arterial pressure (mm. Hg)	116±13	125±21	188±51	171±18
Arterial pressure following inhalation (mm. Hg)	99±16	99±12	161±44	130±15
Per cent decrease arterial pressure	15±6	21±5	14±3	24±6
Control pulse pressure (mm. Hg)	61±6	86±20	100±18	112±32
Pulse pressure following inhalation (mm. Hg)	58±6	65±17	90±17	82±24
Per cent decrease pulse pressure	5±4	24±5	10±2	26±8

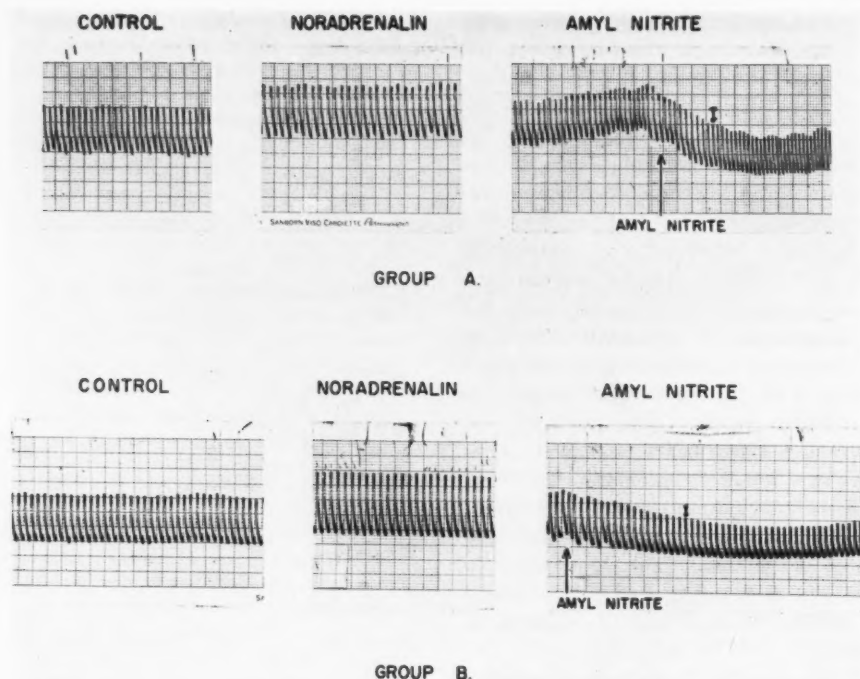


FIG. 1. Femoral arterial pulse pressure tracings of a patient without cardiovascular disease (A) and of a patient with arteriosclerosis with normal arterial pressure (B). Note the decreased bradycrotic response during norepinephrine and greater decrease in pulse pressure following amyl nitrite in B.

of distensibility due to hypertensive or atherosclerotic changes in the wall of the carotid sinus could result in decreased reactivity of the moderator nerves to elevation of blood pressure. The decreased response would be reflected in a diminished bradycrotic response. It has been postulated previously that the decreased bradycrotic response during norepinephrine might be due to an arteriosclerotic process in the walls of the aorta.² Although the data presented here furnish no further proof, a similar explanation might be offered for the decreased bradycrotic response in the patients in groups 2 and 3B presented here. It might be suggested further that the arteriosclerosis present in the patients in group 3A did not involve the walls of the aorta, whereas the arteriosclerotic process in patients in group 3B involved the walls of the aorta.

If one grants the assumption (as Conway and Smith¹ have done) that there is no change in stroke volume immediately following inhalation of amyl nitrite (before the development of tachycardia), it seems reasonable to postulate that changes in the pulse pressure during this period might be an index of elasticity of large vessels. The observation that a greater decrease in pulse pressure following amyl nitrite occurs in the same patients who exhibit a decreased bradycrotic response during infusion of norepinephrine suggests that both responses are a measure of the same abnormality and lends further credence to the hypothesis that such responses might serve as an index of elasticity of large vessels.

It is suggested that these procedures might be useful clinically to document the existence of large vessel sclerosis, which frequently may not be evident by the usual physical examination.

tion and laboratory procedures. Knowledge of the elasticity of large vessels would be particularly important in the evaluation of a hypertensive patient. Since a decreased bradycrotic response during norepinephrine occurs in those patients who exhibit a greater fall in pulse pressure following amyl nitrite, it would seem unnecessary to perform both procedures. The simplicity of procedure—lack of need for arterial puncture—and the ease of interpretation of results would seem to make the response of the heart rate during infusion of norepinephrine the procedure of choice. A reduction in the heart rate of more than 10 beats per minute indicates a normal response and a reduction in the heart rate of less than 4 beats per minute an abnormal response.

SUMMARY

The response of the heart rate during infusion of norepinephrine and of the pulse pressure immediately following inhalation of amyl nitrite was studied in normal, hypertensive, and arteriosclerotic subjects. A greater decrease in pulse pressure following amyl nitrite (>16 per cent) occurred in every patient who exhibited a decreased bradycrotic response during norepinephrine (<4 beats per minute). The differences in pulse pressure and heart rate response were not related to the age of the patient, the control level of arterial pressure, or the per cent increase or decrease in arterial pressure. The factors governing both these responses could not be demonstrated. It had been suggested that a decreased bradycrotic response during norepinephrine might indicate a loss of elasticity of large vessels. The abnormal response to both

procedures in the same patients presented here lends further support to this hypothesis.

SUMMARY IN INTERLINGUA

Le responsa del frequentia cardiac durante le infusion de norepinephrina e le responsa del pression de pulso post le inhalation de nitrito de amylo esseva studiate in subjectos normal, hypertensive, e arteriosclerotie. Un plus importante reduction del pression de pulso post nitrito de amylo (>16 pro cento) occurreva in omne patiente qui exhibiva un reduceite responsa bradycrotic durante norepinephrina (<4 pulsos per minuta). Le differentias in le responsas del pression de pulso e del frequentia cardiac non esseva relateate al etate del patiente, al nivello de controlo del pression arterial, o al augmento o al reduction procentual del pression arterial. Le factores que governa iste duo responsas non poteva esser demonstrate. Il existe le these que un reduceite responsa bradycrotic durante norepinephrina indica possibilmente un perdita de elasticitate in le vasos major. Le hic-presentate observation de responsas anormal a ambe procedimentos in le mesme patiente representa un supporto additional in favor del these mentionate.

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Effect of Valsalva Maneuver on Oxygen Saturation in Patients with Intracardiac Shunts

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Oxygen saturation of arterial and central venous blood was measured continuously during the Valsalva maneuver in patients with and without intracardiac defects. The majority of patients with atrial septal defects and patients with ventricular septal defects and high right ventricular pressure showed a sharp decrease in saturation of radial artery blood shortly after the maneuver. These changes were not recorded accurately by ear oximetry. The patients with shunts uniformly showed a rapid increase in saturation of pulmonary artery blood during the initial period of increased airway pressure. This effect was not observed in patients without shunts. These reactions may be of special diagnostic value under certain circumstances.

ALTHOUGH under "resting" conditions the pressure gradient between the 2 atria is predominantly from left to right, temporary reversals during short periods of the cardiac cycle have been demonstrated in patients^{1,2} and in experimental animals.³⁻⁵ Demonstration by dye-dilution curves of small right-to-left shunts of 5 per cent or less in the majority of patients with atrial septal defects who do not show evidence of gross arterial desaturation⁶ confirmed the theory that these brief periods of reversed gradient are capable of producing shunting of small volumes of venous blood to the left atrium. In 1950, Brecher and Opdyke⁵ demonstrated that various respiratory maneuvers can accentuate this reversal in dogs with experimental atrial septal defects, and in the same year Burchell⁷ reported a pronounced decrease in oxygen saturation of arterial blood during breath holding in a patient with an atrial septal de-

fect associated with a veno-arterial shunt. Variations in oxygen saturation associated with the respiratory cycle have been described in the venous blood of normal persons.⁸ These variations are accentuated in patients with left-to-right shunts and may be observed also in the arterial blood of some of these patients.⁹

In 1954 Lee and co-workers¹⁰ showed that, during the first few heartbeats following the release of increased intrathoracic pressure at the end of the Valsalva maneuver, the right atrial pressure increased above the pulmonary artery wedge pressure and therefore presumably above the left atrial pressure. In 1957 Lee and Gimlette¹¹ reported a diagnostic test for interatrial communications utilizing this effect of the Valsalva maneuver. By means of an ear oximeter, they observed a drop in arterial oxygen saturation which occurred shortly after the period of increased intrathoracic pressure. This was ascribed to the occurrence of a temporary right-to-left shunt.

Since the ear oximeter may not provide a reliable index of arterial oxygen saturation under conditions such as the Valsalva maneuver which cause large changes in the blood content of the ear, the present study was undertaken to confirm the report of Lee and Gimlette¹¹ by means of measurements made directly on arterial blood and to include observations on venous blood.

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Dr. Birkhead was a research fellow of the American Heart Association while he was participating in this study; Dr. Carter was a Medical Research Fellow of the National Research Council, Canada.

MATERIAL AND METHODS

The effect of the Valsalva maneuver on the circulation was investigated in 11 patients with atrial septal defects, 6 with ventricular septal defects, and 10 without shunts, by means of continuous and simultaneous recordings of the oxygen saturation of blood withdrawn both from a systemic artery and from various vessels and chambers of the heart accessible by right heart catheterization. The persons without intracardiac shunts, who served as a control group, included 6 patients referred to the laboratory because of possible cardiovascular lesions and 4 patients with mitral regurgitation. The 6 patients were found to have normal cardiovascular systems on the basis of clinical and catheterization data. Of the 4 patients, 1 patient had severe mitral regurgitation, 1 was studied after a successful mitral valvuloplasty, and the remaining 2 were thought to have mild mitral regurgitation with slight disability. In the latter 2 patients a slight elevation of the pulmonary artery wedge pressure with the V wave representing the maximal pressure was the only abnormality observed in the data obtained by catheterization of the right side of the heart.

The 11 patients with atrial septal defects included 4 with the usual type of defect; 4 with so-called superior vena cava syndrome,¹² which consisted of a high atrial septal defect and anomalous pulmonary venous connection of the right upper and middle lobes to the superior vena cava or right atrium near the juncture of this chamber and the superior vena cava; and 3 patients with atrial septal defect who had unusual dye-dilution curves and may have had partial anomalous pulmonary venous connection in addition to the atrial septal defect. One patient in this group had severe pulmonary hypertension. In the 5 patients who underwent operation, the catheterization findings were confirmed.

The 6 patients with ventricular septal defects included 2 with uncomplicated ventricular septal defect with only slight elevation of the right ventricular systolic pressure and 4 patients with marked right ventricular systolic hypertension, which was due to infundibular pulmonary stenosis in 3 patients and to severe pulmonary hypertension in 1.

The ratios of systolic pressures in the right ventricle to those in the radial artery in these 4 patients averaged 0.90 (range 0.81 to 1.02), indicating that the right and left ventricular systolic pressures were essentially equal.^{13, 14}

Cardiac catheterization was performed in all patients by methods previously described.¹⁵⁻¹⁷ These included pressure, oxygen saturation, and dye-dilution studies. The patients rested in the

supine position. They had a light meal prior to the procedure and received premedication of 90 mg. (1½ gr.) of secenal sodium and 30 mg. (½ gr.) of codeine.

The Valsalva maneuver was performed as follows: the patients were asked to take a deep breath and to blow from their lungs (glottis open) into a mouthpiece connected by tubing to a strain-gage and to an aneroid manometer (Tycoos), so as to maintain a pressure of 40 mm. Hg as indicated on the dial of the aneroid manometer which was placed in their field of vision. This increased airway pressure was maintained for about 15 seconds. The precise measurements of the photographic records of the airway pressure revealed that the average mean pressure during the pressure plateau was 37 mm. Hg (range 21 to 48) and, excluding 2 patients with extreme values, the range was 31 to 44 mm. Hg. The mean duration of the pressure rise was 17 seconds (range 12.3 to 20.6 seconds).

For about 30 seconds prior to the beginning of the maneuver, during the period of increased airway pressure, and for 20 to 40 seconds following the maneuver, arterial oxygen saturation was recorded continuously by an ear oximeter and also directly in arterial blood being withdrawn continuously through a cuvette oximeter attached to an indwelling no. 20-gage needle in the radial artery. In addition, in most cases the oxygen saturation was recorded continuously in blood being withdrawn through a second cuvette oximeter via a catheter the tip of which was placed at selected sites in a vessel or chamber on the right side of the heart. The average rate of flow through the cuvette oximeters was 20.0 ml. per minute with a range of 10.2 to 37.7 ml. per minute. The variables, which included airway pressure, respiration, electrocardiogram, heart rate, and the oxygen saturation of blood in the ear, radial artery, and in most cases from the right side of the heart, were recorded by a photokymographic assembly¹⁵ on paper 18 inches wide moving at a speed of 0.5 cm. per second. Each milliliter of blood flow through the cuvette oximeters was signaled on the photographic record. The time required for the blood to traverse the "dead space" volume between the sampling site in the vascular system and the detecting element of the cuvette oximeters was calculated from the flow rate and the volume of the needle-oximeter or catheter-oximeter assembly. With the use of this correction factor the curves of blood oxygen saturation recorded from the right side of the heart and the radial artery were aligned, with respect to time, with the other recorded variables, so that simultaneously occurring values could be compared throughout the period

TABLE 1.—*Number of Recordings of Oxygen Saturation of Blood Withdrawn from Various Sites during the Valsalva Maneuver*

Group	Number of patients	Radial artery	Pulmonary veins	Pulmonary artery	Right atrium	Superior vena cava
Without shunts	10	10	—	9	—	—
With atrial septal defects	11	25	5	10	—	8
With ventricular septal defects	6	8	—	5	2	—

of observation. The average volume of the sampling systems from the needle tip in the radial artery up to and including the detecting chamber in the cuvette oximeter was 0.19 ml. (range 0.18 to 0.30 ml.), whereas the volume for the cardiac catheter-cuvette systems averaged 1.53 ml. (range 1.28 to 2.48 ml.). The time corrections for these arterial and venous sampling systems averaged 0.6 second (range 0.3 to 1.2 second) and 4.9 seconds (range 2.7 to 8.6 seconds) respectively.

The values for blood oxygen saturation were measured in all records at selected points with reference to the period of increased intrathoracic pressure. These included maximal, minimal, and average saturation values during the control period prior to the beginning of the maneuver; the values at 5, 10, and 14 seconds following the onset of increased airway pressure; and the values at 10, 20, and 30 seconds following the end of the period. In addition, when present, the following saturation values and the time at which they occurred were measured: (1) the maximal saturation reached during the maneuver, (2) the onset of the decrease (dip) after the release of the increased intrathoracic pressure, and (3) the minimal value during this decrease. Because of cyclic respiratory changes in oxygen saturation during the control period, decreases or increases in saturation of less than 1 per cent were not considered to be significant in relation to variations induced specifically by the Valsalva maneuver.

The appearance times of dye-dilution curves recorded at the radial artery following the injection of the indicator into the superior or inferior vena cava in patients with right-to-left shunts were measured and correlated with the onset of the decrease in the radial artery saturation following the Valsalva maneuver. In patients in whom a left-to-right shunt but no right-to-left shunt was evident in the dye-dilution curves, the appearance time of a "potential" right-to-left shunt was esti-

mated by subtracting the pulmonary recirculation time measured from the curve from the appearance time at the radial artery following the injection into a vena cava.

The sites in the central circulation from which the blood oxygen saturation was recorded included the pulmonary artery, pulmonary vein, right atrium, and superior vena cava. The number of maneuvers with records of saturation from these various sites in the 3 groups of patients is shown in table 1. Recordings of the oxygen saturation of radial artery blood during the Valsalva maneuver were obtained in all patients and those of pulmonary artery blood in all but 3.

RESULTS

Typical changes in the oxygen saturation in arterial blood recorded by the ear and cuvette oximeters in 2 patients with atrial septal defects are shown in figure 1. In one of these patients the ear oximeter curve followed closely the actual pattern of changes in arterial saturation as recorded by the cuvette oximeter directly from radial artery blood while in the other, the ear oximeter record did not accurately reflect the changes evident in the radial artery saturation. The latter was the case in about 50 per cent of the experiments and therefore the ear oximeter records were not analyzed further.

The average values and changes in oxygen saturation of radial and pulmonary artery blood and their variability before, during, and after the Valsalva maneuver in patients without shunts and in those with atrial septal defects are shown in figure 2. Examples of original recordings from individual patients are shown in figure 3. An increase in systemic arterial saturation occurred uniformly during the period of increased intrathoracic pressure and was similar in magnitude in all 3 groups. It amounted to 1.1 per cent (range 0.5 to 4.5 per cent), 1.5 per cent (range 0.5 to 4.0 per cent), and 1.8 per cent (range 0.5 to 3.5 per cent) above the maximal control value for patients without shunts and with atrial and ventricular septal defects respectively. Usually within 10 seconds after the release of the increased pressure a sudden decrease was clearly evident in radial artery saturation in patients with atrial septal defects, whereas

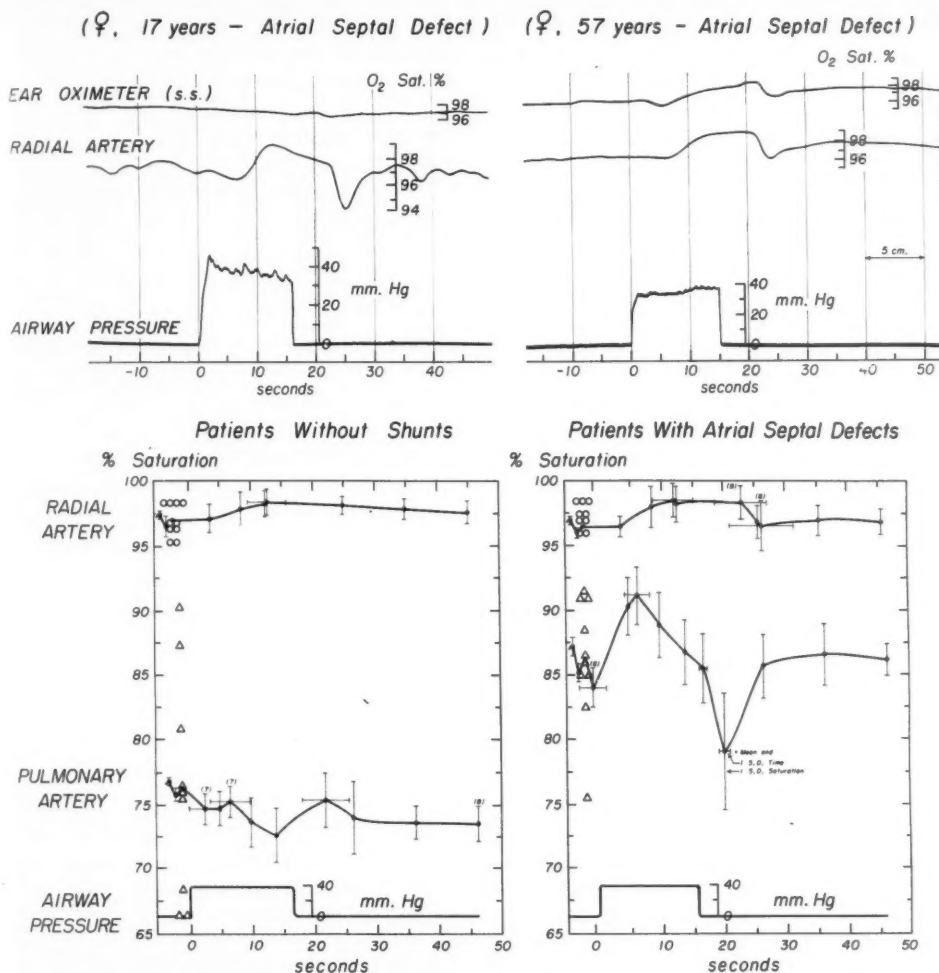


FIG. 1 Top. Comparison of changes in oxygen saturation of systemic arterial blood recorded continuously during the Valsalva maneuver by an earpiece oximeter and a cuvette oximeter connected to a radial artery. The patient whose record is shown in the left panel may possibly have anomalous pulmonary venous connection in addition to the atrial septal defect. The patient whose record is shown in the right panel has a high atrial septal defect with anomalous connection of the right upper and middle lobes to the junction of the right atrium and superior vena cava.¹² Note that the recordings from the earpiece and cuvette oximeter in the right panel correspond closely, but the earpiece record in the left panel fails to show the changes actually occurring in oxygen saturation of arterial blood as indicated by the cuvette oximeter.

FIG. 2 Bottom. Average and variability of the changes in oxygen saturation of blood withdrawn from the radial and pulmonary arteries in 10 subjects without intracardiac shunts and 10 patients with atrial septal defects. Black circles, average of the group calculated from changes in per cent saturation from the average control value for each patient. Numbers in brackets, number of patients, if the given point is not based on all the patients of the group. Vertical and horizontal bars, 1 standard deviation for the saturation and time values respectively. The points that precede the onset of the increase in airway pressure represent the maximal, minimal, and average control saturation for the group. Open circles and triangles, the average saturation values of radial and pulmonary artery blood of individual patients during the control period. Note the dip in the radial artery saturation shortly after the end of the increased airway pressure and the biphasic response in the pulmonary artery saturation in patients with atrial septal defects and the absence of these changes in patients without shunts.

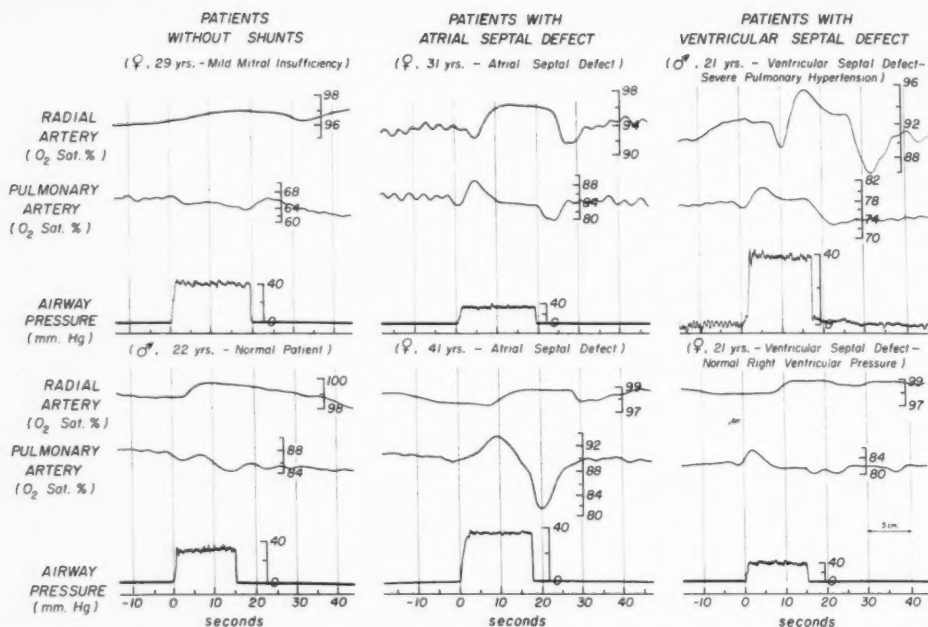


FIG. 3. Photographic recordings of the oxygen saturation of systemic and pulmonary artery blood during the Valsalva maneuver in patients with and without intracardiac defects. The patient with atrial septal defect whose record is shown in the upper panel may possibly have an anomalous pulmonary venous connection in addition to atrial septal defect. Note: 1. The increase in saturation of radial artery blood during the period of increased airway pressure in each patient. 2. The rapid decrease in radial artery saturation shortly after the release of increased airway pressure in the patients with atrial septal defects and in the patient with ventricular septal defect and pulmonary hypertension in contrast to the gradual decrease in the patients without defects and in the patient with ventricular septal defect and no right ventricular hypertension. 3. The clearly evident biphasic response in saturation of pulmonary artery blood in the patients with shunts, characterized by a rapid increase shortly after the onset of increased airway pressure followed by a decrease to below control values after the maneuver, in contrast to the decrease below control values throughout the period of increased airway pressure in the patients without shunts.

the saturation in the cases without shunts generally exhibited a slow return toward control levels. An early decrease in saturation of 1 per cent or more following the Valsalva maneuver was found in 8 of 11 patients with atrial septal defects and in 3 of 10 patients without shunts. One of the 3 patients with atrial septal defects who did not show the usual response showed a larger decrease in saturation during a subsequent maneuver, and the lack of a typical response in another patient may have been related to a 16-second period of apnea that followed the Valsalva

maneuver. In the 3 patients without shunts who showed a 1-per cent decrease in saturation after the maneuver, the decrease was more gradual than in patients with interatrial communications in whom the decrease was sharp, the contour of the change in saturation resembling somewhat that of an indicator-dilution curve. In 6 of 8 patients with atrial septal defects who exhibited this characteristic response, the sudden decrease in saturation ranged from 2.5 to 4.5 per cent, whereas it amounted to 1 per cent in the remaining 2 patients and in the 3 patients without shunts

When the magnitude of the decrease in per cent saturation was divided by the time in seconds from the onset to the minimal value during the "dip," the values for the 3 patients without shunts fell between 0.10 and 0.20 and those for the 8 patients with atrial septal defects fell between 0.25 and 1.25; these values confirmed the visual impression of a more rapid decrease in saturation in patients with atrial septal defects. The type of atrial septal defect and the presence or absence of anomalous pulmonary venous connection did not seem to influence the response.

The responses of 2 patients with ventricular septal defects are also shown in figure 3. The patient with right ventricular systolic hypertension showed a sharp dip in the radial artery saturation after the maneuver. This type of response was found in all 4 patients with right ventricular systolic hypertension, whether due to pulmonary stenosis or pulmonary hypertension, and the magnitude of the decrease ranged from 1.5 to 9 per cent. The 2 patients without ventricular hypertension showed only a gradual slow decrease in the radial artery saturation similar to the response seen in the patients without shunts (fig. 3).

The relation of the time from the end of the Valsalva maneuver to the onset of the dip in radial artery saturation, to the appearance time of an actual or "potential" right-to-left shunt of a dilution curve recorded at the radial artery in patients with intracardiac defects is illustrated in figure 4. There is a general correlation of the 2 variables suggesting that this dip in arterial oxygen saturation may be caused by the transient occurrence of, or increase in, an existing right-to-left shunt.

Striking differences in the changes in oxygen saturation of pulmonary artery blood associated with the Valsalva maneuver were observed between the patients with and those without intracardiac shunts. The average values and their variability obtained in the groups without shunts and with atrial septal defects are shown in figure 2. The characteristic biphasic response in patients with defects

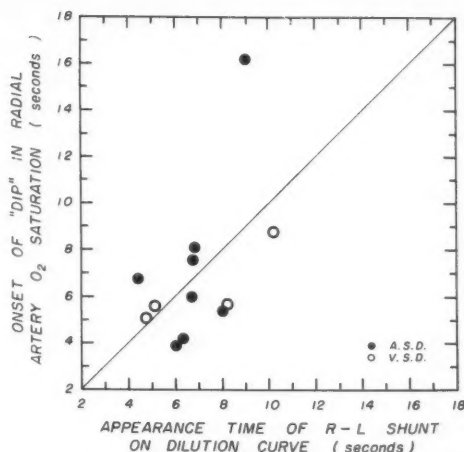


FIG. 4. Correlation of the appearance time of the right-to-left shunt deflection in dye-dilution curves recorded following injection of indicator into the vena cava with the time from the cessation of the Valsalva maneuver to the onset of the dip in arterial oxygen saturation after the Valsalva maneuver. Note the general correlation of the 2 variables suggesting that the dip in arterial oxygen saturation in these patients is due to the transient occurrence or increase in a pre-existing right-to-left shunt that occurs concomitantly with the cessation of the Valsalva maneuver.

and its absence in patients without shunts is well illustrated by original records from individual patients shown in figure 3. All the patients with atrial and ventricular septal defects exhibited a definite increase in pulmonary artery saturation above the maximal control value during the initial period of increased intrathoracic pressure, which averaged 4.0 per cent (range 1.0 to 7.0 per cent), and 4.2 per cent (range 2.0 to 9.5 per cent) respectively. In 8 of 10 patients with atrial septal defects the increase in saturation of pulmonary artery blood was preceded by a definite small dip below the minimal control value occurring just before, or approximately at the time of, the onset of increased airway pressure. This phenomenon was seen in only 1 patient with ventricular septal defect. The peak saturation during the maneuver was followed by a decline that reached saturations below minimal control values in 4 of 15 pa-

tients with intracardiac defects during the later stages of the period of increased intrathoracic pressure. The second part of the biphasic response was a sudden further decrease in saturation to levels below the minimal control values beginning at the time of the release of the increased airway pressure. This further decrease was observed in all patients with atrial septal defects and in 4 of 5 cases of ventricular septal defect and averaged respectively 6.4 per cent (range 3.5 to 16.0 per cent), and 3.2 per cent (range 1.0 to 6.0 per cent).

In contrast to the patients with intracardiac shunts, those without shunts showed only a decrease in saturation of pulmonary artery blood during the period of increased intrathoracic pressure. In 7 of 9 cases this decrease was interrupted by a temporary return toward the control value followed by a second more pronounced decrease to lower saturation levels (figs. 2 and 3). All patients in this group exhibited a wave of increase in saturation starting usually at the time of release of increased airway pressure before the saturation returned to a steady plateau. The maximal saturation of this wave was below, above, or equal to the control values in various patients.

The oxygen saturation of blood withdrawn from the superior vena cava was recorded during the Valsalva maneuver in 8 patients with atrial septal defects. A pronounced increase in the saturation ranging from 3.5 to 12.5 per cent occurred during the period of increased intrathoracic pressure in 5 of the 8 patients, whereas in the remaining 3 there was only a decrease in saturation very similar to the change that took place in the pulmonary artery of patients without shunts. Two patients who showed this increase and one who did not show it, had an anomalous pulmonary venous connection at the junction of the superior vena cava and the right atrium suggesting that this increase in saturation may have been due to backflow of arterialized blood into the superior vena cava from the right atrium.

A significant increase in the saturation of right atrial blood was not observed during the Valsalva maneuver in the 2 patients with ventricular septal defect in whom this was recorded.

The oxygen saturation of blood withdrawn from a pulmonary vein was recorded during the Valsalva maneuver in 5 patients with atrial septal defect. In 4 cases these veins were anomalously connected. In 2 cases, 1 of which is illustrated in figure 5, there was a sudden decrease in oxygen saturation of blood in the pulmonary vein shortly after the maneuver, although a definite dip in the radial artery saturation could be seen. One patient did not show this decrease at either sampling site, whereas in the remaining 2 the dip was present in the pulmonary vein and in the radial artery saturation.

The reproducibility of the saturation changes in response to the Valsalva maneuver can be gaged from figure 6, which shows the magnitude and the time of maximal saturations in the radial artery from successive maneuvers in the same patients. These data are based on patients with shunts, in several of whom the saturation in the radial artery was recorded 2 or 3 times simultaneously, with the saturation from different sampling sites reached by the cardiac catheter. Most of the points fall on or close to the line of identity, usually within 0.5 per cent saturation and 2.0 seconds. Occasionally, however, larger differences were observed.

DISCUSSION

Continuous recording of the oxygen saturation of blood being withdrawn simultaneously from a systemic artery and from various sites on the right side of the heart allows a better understanding of the circulatory changes that occur in patients with intracardiac shunts during the Valsalva maneuver than has been possible previously. It also permits a better evaluation of diagnostic tests that utilize this maneuver.¹¹

Although a sharp decrease in radial artery saturation was found shortly after the end of

(♀, 51 years - Atrial Septal Defect with Pulmonary Hypertension)

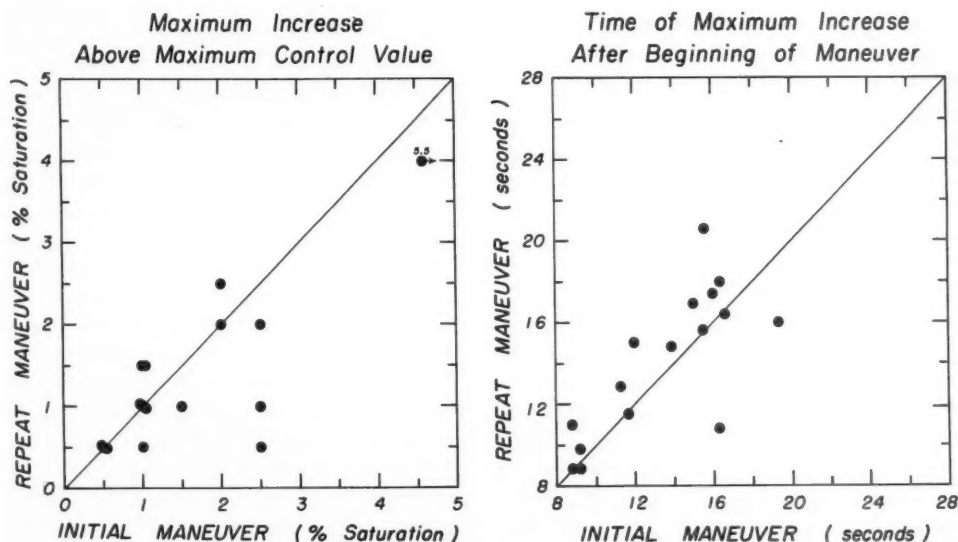
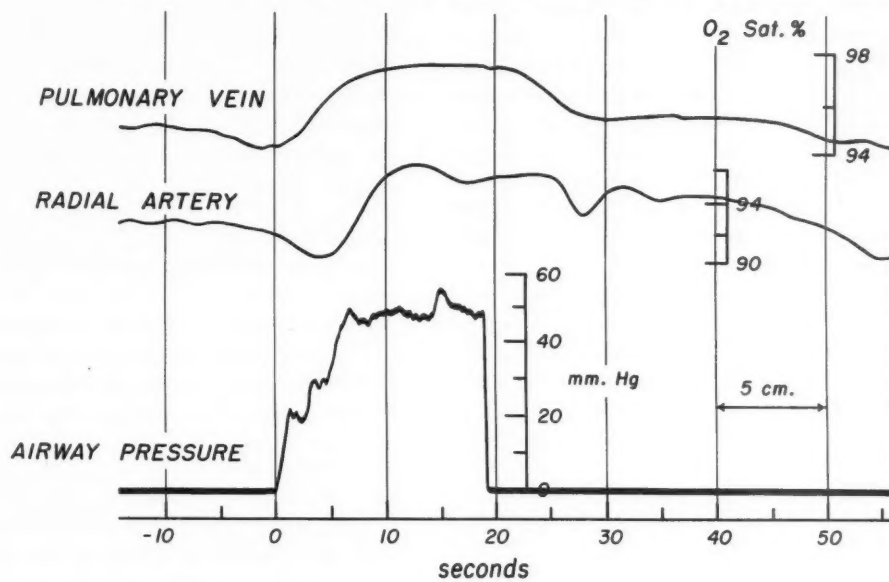


FIG. 5 *Top*. Comparison of changes in the oxygen saturation of pulmonary vein and radial artery blood during the Valsalva maneuver. Note the definite dip in saturation of radial artery blood shortly after the release of increased airway pressure and its absence in pulmonary vein blood indicating that this decrease in saturation of arterial blood is due to a right-to-left shunt rather than to a change in oxygenation of the blood traversing the lungs.

FIG. 6 *Bottom*. Reproducibility of the magnitude and time of maximal saturation of radial artery blood recorded during successive Valsalva maneuver in the same patients.

the Valsalva maneuver in the majority of patients with atrial septal defects as reported by Lee and Gimlette,¹¹ ear oximetry, which they utilized, was found to be unreliable for this purpose. In about half of the experiments ear oximeter records did not reflect accurately the saturation changes evident in the radial artery blood and were impossible to interpret. This would be expected under the conditions of large and rapid changes in blood content of the ear that are produced by the Valsalva maneuver. Because compensation for the changes in quantity of transilluminated blood is not complete,¹⁸ artifacts are produced in the oxygen saturation values indicated by the ear oximeter under these circumstances.

Continuous recording of oxygen saturation of systemic arterial blood withdrawn through a cuvette oximeter during the Valsalva maneuver may provide a screening test for the presence of certain types of defects. However, even the demonstration of a typical response does not differentiate between patients with ventricular septal defects with high right ventricular pressure and patients with atrial septal defects. It is probable that patients with aortopulmonary communications and pulmonary hypertension also may exhibit this type of response. Furthermore, the test would not provide information as to whether the interatrial communication is of the ostium primum or secundum type and whether or not it is associated with anomalous pulmonary venous connection. The latter type of information is often essential in planning the surgical attack on the underlying lesion.

A temporary right-to-left shunt shortly after the end of the Valsalva maneuver might be expected to occur on the basis of changes in interatrial pressure gradient as demonstrated in human beings¹⁰ and in experimental animals.⁵ The finding that in 2 patients the dip in the radial artery saturation occurred while there was no sharp decrease in the pulmonary vein saturation suggests that the dip in systemic arterial saturation is not due to an effect of the maneuver on the oxygenation of blood during its passage through the lungs. Reversal of flow in the vena cava and its trib-

utaries^{19,20} probably accounts for the finding of the decrease in saturation in the anomalously connected pulmonary veins in the other 2 patients. Correlation between the appearance time of the deflection caused by the right-to-left shunt of a dilution curve²¹ recorded at the radial artery and the time of onset of the dip in the radial artery saturation following the Valsalva maneuver also supports the concept that the dip in the radial artery saturation is due to a temporary appearance of, or an increase in magnitude of, a right-to-left shunt.

Present experiments confirmed the finding of the increase in systemic arterial saturation during the period of increased intrathoracic pressure, which Lee and Gimlette¹¹ ascribed to a decrease in the pre-existing right-to-left shunt. However, the fact that this increase was of similar magnitude in patients with and without intracardiac defects suggests that other factors must play a part in most cases. Possible causes of the increase in arterial oxygen saturation include (1) increase in alveolar pO_2 resulting from the increase in intrathoracic pressure and augmented ventilation of some of the alveoli associated with the deep inspiration preceding the maneuver, and (2) decrease in carbon dioxide content of arterial blood due to this deep inspiration which would shift the hemoglobin saturation curve to the left.

Changes in oxygen saturation of the blood withdrawn from various sites on the right side of the heart are of interest. All patients with atrial septal defects exhibited similar changes in the pulmonary artery saturation during the Valsalva maneuver. The initial dip in saturation is probably due to an increased inflow of the blood from the systemic veins associated with the deep inspiration²² that preceded the increase in airway pressure, whereas the rise in saturation during the period of increased intrathoracic pressure must be related to the decrease in systemic venous return well known to occur during the Valsalva maneuver.^{19, 20, 23-25} The increase in saturation could result if the volume of blood shunted from left to right increased, re-

ained unchanged, or decreased but to a lesser degree than the decrease in systemic venous return. The decline in pulmonary artery saturation later during the period of increased intrathoracic pressure could result from an increase in systemic venous return, a decrease in the volume of the left-to-right shunt, or both.

The sudden further decrease in the pulmonary artery saturation, practically coincident with the release of increased pressure, must be due to the sudden onrush of systemic venous blood to the right atrium which increases the right atrial pressure, decreases the absolute volume of the left-to-right shunt, and creates a temporary right-to-left shunt as indicated by the changes in the radial artery saturation.

The sharp rise in the superior vena cava saturation that occurred in 5 of 8 patients with atrial septal defects, 3 of whom did not have anomalous pulmonary veins connected close to the superior vena cava, is probably due to the reversal of flow known to occur in the venae cavae during the Valsalva maneuver.^{19, 20}

The patients without shunts showed only a decrease in the pulmonary artery saturation during the period of increased intrathoracic pressure. This may be due to the decrease in the return of the blood from the venae cavae and thus an increase in the proportion of the low-saturation blood from the coronary sinus contributing to the total pulmonary flow, since a decrease in the coronary return would not be expected initially due to the increase in the intrathoracic pressure. The temporary return of pulmonary artery saturation toward, but not above, the control values during the early part of the period of increased intrathoracic pressure might be related to basic changes in the contribution of the superior and inferior caval blood of different saturations to the total venous return.

In accord with the findings of Lee and Gimette,¹¹ the 2 patients with ventricular septal defects without pronounced elevation of the right ventricular pressure did not show the characteristic dip in radial artery saturation

found in patients with atrial septal defects. However, the differential, diagnostic value of this finding is limited, since a definite decrease was found in all 4 patients with ventricular septal defects associated with right ventricular systolic hypertension. In such patients an increase of right ventricular pressure above that of the systemic arteries may occur during the Valsalva maneuver.²⁶ All 6 patients with ventricular septal defects exhibited an increase in pulmonary artery saturation similar to that found in patients with atrial septal defects; however, this increase in saturation was not observed in the right atrium.

The findings of the characteristic saturation changes on the right side of the heart during the Valsalva maneuver may be of some diagnostic help during right heart catheterization since, by repeating the maneuver with continuous sampling at various sites, it should be possible to demonstrate and localize the left-to-right shunt. As demonstrated in 2 cases of ventricular septal defect, the characteristic increase in oxygen saturation of right heart blood should be present at and downstream to the site of the shunt, but not upstream to it in the absence of valvular regurgitation. This method is not likely to prove more sensitive than other ways of detection of left-to-right shunts in the majority of cases. However, in patients in whom the left-to-right shunt may be too small to demonstrate by other methods under normal resting conditions, either due to the extremely small size of the defect or due to severe pulmonary hypertension resulting in a balanced right-to-left and left-to-right shunt, temporary "unbalancing" of the shunt in the left-to-right direction by increasing the airway pressure may prove to be of special diagnostic value.

SUMMARY

Changes in blood oxygen saturation during the Valsalva maneuver were recorded continuously and simultaneously in blood being withdrawn from the radial artery and from various sites on the right side of the heart in patients with and without intracardiac defects.

A transient decrease in oxygen saturation of radial artery blood was clearly evident shortly after the termination of the increased airway pressure in 8 of 11 patients with atrial septal defects and in 4 patients with ventricular septal defects and right ventricular systolic hypertension. This response was not observed in 10 patients without shunts nor in 2 patients with ventricular septal defects without marked elevation of right ventricular pressure.

However, ear oximeter records did not reflect accurately the saturation changes evident in the radial artery blood under these circumstances and hence were of limited diagnostic value. This is probably because of incomplete compensation of this instrument for the large and rapid changes in the blood content of the ear caused by the Valsalva maneuver.

Correlation between the appearance time of the deflection due to the right-to-left shunt of dye-dilution curves and the time of onset of the decrease in arterial saturation following the Valsalva maneuver, and comparison of the changes in oxygen saturation of pulmonary vein and radial artery blood during the maneuver suggest that the decrease in the systemic arterial saturation is due to the temporary occurrence of, or a transient increase in the magnitude of, a right-to-left shunt.

All the patients with intracardiac defects showed characteristic biphasic changes in the oxygen saturation of pulmonary artery blood consisting of clearly evident rapid increase in saturation shortly after the onset of increased airway pressure followed by a decrease which was sharply accentuated shortly after the release of airway pressure. In contrast only a decrease in saturation was observed in patients without shunts.

These characteristic changes in oxygen saturation of blood from the pulmonary artery in patients with left-to-right shunts were absent when venous blood was sampled from chambers in the right heart upstream to the defect. These responses allow a better understanding of the changes in the circulation of patients with intracardiac defects during the Valsalva maneuver and may be of diagnostic

value in detecting and localizing cardiac defects under certain circumstances.

ACKNOWLEDGMENT

These studies were made possible by the unstinting co-operation of many technical and professional colleagues to whom the authors are indebted.

SUMMARY IN INTERLINGUA

Alterationes del saturation oxygenic esseva registrate continue e simultaneemente durante le effectuation del manovra de Valsalva in specimens de sanguine prendite ab le arteria radial e ab varie sitos al latere dextere de corde de patientes con e sin defectos intra-cardiac.

Un reduction transiente del saturation oxygenic del sanguine ab le arteria radial esseva clarmente evidente un breve tempore post le termination del augmentate pression in le vias aeree in 8 del 11 patientes con defectos atrio-septal e in 4 patientes con defectos ventriculo-septal e hypertension systolic dextero-ventricular. Iste responsa non esseva observate in 10 patientes sin shunting intra-cardiac e non in 2 patientes con defectos ventriculo-septal non associate con marcate grados de elevation del tension dextero-ventricular.

Tamen, lecturas del oxymetro de aure non reflecte accuratemente le alterationes del saturation oxygenic que es evidente in le sanguine del arteria radial sub iste circumstantias. Per consequente illos es de pauco valor diagnostic. Le causa de iste facto es probabilemente le incomplete compensation que iste instrumento provide pro le grande e rapide alterationes del contento de sanguine in le aure que es causate per le manovra de Valsalva.

Le correlation inter le tempore del apparition del deflexion effectuate in curvas de dilution de colorante per shunting dextero-sinistre e le tempore del declaration del reduction in le saturation arterial que occorre post le manovra de Valsalva, insimul con un comparison del alterationes in le saturation oxygenic del sanguine in le venas pulmonar con illos del sanguine in le arteria radial durante le manovra, suggere que le reduction del saturation oxygenic in le sanguine del

terias systemic es causate per un occurren-
a temporari de un shunting dextero-sinistre
per le transiente augmento de su magnitudine.

Omne le patientes con defectos intracardiac
chibiva characteristic alterationes biphasic
el saturation de oxygeno in le sanguine pul-
mono-arterial, consistente de un clarmente
vidente e rapide augmento del saturation
brevemente post le declaration del augmentate
pression in le vias aeree, sequite per un redu-
cion del saturation que esseva accentuate
seutemente un breve intervallo post le relaxa-
cion del pression in le vias aeree. Per contrasto
con isto, solamente le reduction del saturation
esseva observate in patientes sin shunting
intracardiac.

Iste characteristic deviationes del satura-
tion oxygenic in le sanguine del arteria pul-
monar in patientes con shunting sinistro-dex-
tere esseva absente quando specimens de
sanguine venose esseva prendite ab cameras
in le parte dextere del corde ubi le fluxo de
sanguine haveva non ancora passate per le
defecto. Le responsas notate permette un plus
precise comprehension del alterationes in le
circulation de patientes con defectos intra-
cardiac, occurrente durante le manovra de
Valsalva, e es possiblement de valor diag-
nostic in le detection e localisation de defectos
cardiac sub certe circumstantias.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Bell's Palsy and the respiratory nerve of Bell were described by Charles Bell (1774-1842) in a communication read July 12, 1821, by Sir Humphry Davy before the Royal Society of London, entitled "On the Nerves, giving an account of some experiments on their structure and functions, which lead to a new arrangement of the system." This appears in the *Philosophical Transactions of the Royal Society of London*, second part for 1821, pp. 398-424.

After describing the "respiratory nerve of the face, being that which is called the *portio dura* of the seventh" and detailing his experiments, he says:

"We have proofs equal to experiments, that in the human face the actions of the muscles which produce smiling and laughing, are a consequence of the influence of this respiratory nerve. . . .

"Cases of this partial paralysis must be familiar to every medical observer. It is very frequent for young people to have what is vulgarly called the blight; by which is meant, a slight palsy of the muscles on one side of the face, and which the physician knows is not formidable. Inflammations of glands seated behind the angle of the jaw will sometimes produce this. All such affections of the respiratory nerve will now be more easily detected; the patient has a command over the muscles of the face, he can close the lips, and the features are duly balanced; but the slightest smile is immediately attended with distortion, and in laughing and crying the paralysis becomes quite distinct. The knowledge of the sources of expression teaches us to be very minute observers."

Successful Surgical Repair of Aortic Insufficiency Due to Valvular Fenestration

By C. P. BAILEY, M.D., ALBERT N. BREST, M.D., NICOLAS DONTAS, M.D., AND J. F. URICCHIO, M.D.

AORTIC valvular fenestration is a common anatomic finding that has been considered to be of little clinical importance. On occasion this defect may permit a major degree of regurgitation, however, with resultant dynamic aortic insufficiency. Until recently little consideration could be given to anatomic correction of aortic valvular insufficiency. However, with the advent of open-heart surgery it has become possible to devise surgical techniques for direct repair of this lesion.¹ This report deals with the successful surgical repair of aortic valvular fenestration by use of complete cardiopulmonary bypass.

CASE REPORT

H.M., a 29-year-old white man, had a heart murmur since birth. He was asymptomatic, however, until age 25 when he had a bout of bacterial endocarditis. Following this illness he developed dyspnea on exertion and increasing ease of fatigability; in April 1958 he began to note exertional angina pectoris which was relieved by rest and nitroglycerin. He did not complain of orthopnea, cough, syncope, or peripheral edema.

The pertinent physical findings were limited to the cardiovascular system. The blood pressure was 130/0. The peripheral pulses were bounding. The heart rate and rhythm were normal. A grade IV, rough aortic systolic murmur was widely transmitted over the precordium, followed by a grade III blowing aortic diastolic murmur. The point of maximal apical impulse was visible in the sixth interspace along the anterior axillary line. There were no evidences of congestive failure.

The electrocardiogram revealed left ventricular hypertrophy and the chest x-ray showed 2- to 3-plus enlargement of the left ventricle. Suprasternal thoracic aortography demonstrated the

presence of 3-plus aortic regurgitation (fig. 1).

On February 3, 1959, cardiac surgery was performed with use of complete cardiopulmonary bypass with cannulation and direct antegrade perfusion of the coronary arteries. A large central fenestration was found in the left aortic cusp and the commissural portion of the valve between the right and left coronary bearing cusps were thickened and calcific. The margin of the right cusp was thickened and retracted, and tended to become prolapsed. The noncoronary cusp was normal (fig. 2).

A patch of formalinized polyvinyl sponge (Ivalon) 3 mm. thick was tailored and utilized to repair the valvular fenestration by application into the concavity of the left cusp with circumferentially placed mattress sutures. The right and left coronary cusps were united to form a bicuspid valve (fig. 2).

The patient had an uncomplicated postoperative course. The blood pressure became stabilized at 130/60 and the aortic murmurs diminished in intensity to grade-II systolic and grade-I diastolic. Thoracic aortography by way of a catheter revealed a residual 1-plus regurgitation (fig. 1).

DISCUSSION

Cardiac valvular fenestration has long been recorded as a common anatomic finding at postmortem examination. Friedman and Hathaway² made observations on the appearance of the semilunar valves in 342 autopsies and recorded an incidence of fenestration of 72 per cent. Foxe³ studied 300 successively observed hearts, and found valvular fenestration in 82 per cent. The aortic and pulmonary valves were involved almost equally.

The exact cause of this lesion is not clear. It may be due to a congenital tissue defect, since Foxe found fenestrations to be present in fetal hearts. Usually there is no histologic evidence of inflammation. Friedman and Hathaway suggest that it is a form of atrophy that may begin in early childhood, or even in the fetus, and that aging, dilatation of the

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FIG. 1. Preoperatively, a 3-plus regurgitation was demonstrated by suprasternal thoracic aortography (*middle*). A striking reduction in the aortic insufficiency was demonstrated post-operatively by catheter thoracic aortography (*right*). Control study, before dye injection, is on *left*.

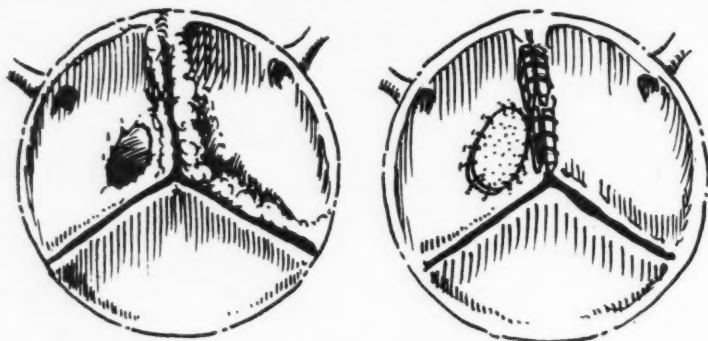


FIG. 2. Schematic representation of the valvular pathology before (*left*) and after (*right*) surgical repair.

ring, and increased intravascular pressure may be contributing factors.

In spite of the frequency of this defect it has not aroused very much attention among clinicians. Frequently, even at autopsy, this finding is left unrecorded, presumably because of the prevalent feeling that the lesion does not have any clinical significance.

Diastolic "functional" murmurs occurring at the base of the heart have been reported for many years. They have been associated with systemic and pulmonary hypertension, fever, anemia, and hyperthyroidism. Garvin⁴ found a diastolic aortic murmur in 7 per cent of hypertensive patients in a survey of 200 consecutive cases. The Graham Steell murmur has long been regarded as the classical mur-

mur of functional pulmonic insufficiency.

Fenestration of the semilunar cusps may or may not give rise to basal diastolic murmurs; and even in the presence of murmurs, these valvular lesions generally are unimportant clinically. The presence or absence of an audible murmur in valvular fenestration depends primarily upon the location of the defect. When the lesion is located near to the cusp margins, the fenestration is closed off during diastole by apposition of the adjacent leaflets. Under ordinary circumstances regurgitation will occur only if the central portion of the cusp is involved. Under conditions of hypertension or dilatation of the ring, however, failure of the closing cusps to approximate with the usual margin of overlap may

permit the fenestration to become functional.

Although these defects are generally not important clinically, dynamic aortic insufficiency may occur on occasion, perhaps as a result of rupture of connecting tissue bands separating smaller fenestrations, with consequent enlargement of the defect. Another cause for enlargement of the defect is acute inflammatory change involving the fenestration. It is believed that this latter mechanism, e., bacterial endocarditis engrafted upon a congenital defect was an important contributing factor to the dynamic aortic insufficiency in the present case.

The valvular regurgitation in this patient was adequately repaired by use of an Ivalon patch to close the fenestration plus surgical union of the right and left coronary cusps to form a conjoined aortic valve cusp. Thus, a bicuspid aortic valve was created. Although a minor degree of residual aortic insufficiency was demonstrated postoperatively by thoracic aortography, it is not expected to be significant clinically.

SUMMARY

A case of dynamic aortic insufficiency due to valvular fenestration is described. The defect was successfully repaired with an Ivalon patch to close the fenestration plus the surgical creation of a bicuspid aortic valve.

SUMMARIO IN INTERLINGUA

Es describe un caso de dynamic insufficiencia aortic causate per fenestration valvular. Le defecto esseva reparate a bon successo. Le fenestration esseva claudite per medio de un pittacio de Ivalon. Un bicuspide valvula aortic esseva create chirurgicamente.

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Therefore from these, and many such things as these, it is clear, that those things which are before spoken by former Authors concerning the motion and use of the heart and the arteries do either seem inconvenient or obscure, or admit of no compossibility, if one do diligently consider them; therefore it will be profitable to search more deeply into the business, and to contemplate the motions of the arteries and heart, not only in man, but also in all other creatures that have a heart; as likewise by the frequent dissection of living things, and by much ocular testimony to discern and search the truth.—WILLIAM HARVEY. *De Motu Cordis*, 1628.

Abscess of the Heart

A Complication of Acute Vegetative and Ulcerative Endocarditis

By ALFRED ZETTNER, M.D., AND VICTOR J. IRMIERE, M.D.

At autopsy we encountered a large abscess of the interatrial septum as a complication of acute vegetative and ulcerative endocarditis, which was probably bacterial. The abscess was connected by a fistula to the aorta and furthermore had ruptured into the left atrium. A search of the literature failed to disclose a similar lesion.

ABSCCESS of the heart, as any abscess elsewhere in the body, develops in 2 principal ways: (1) by dissemination from a distant infectious focus, (2) by direct extension of an infectious process located in the heart itself. Myocardial abscess due to dissemination of infection or septicemia was found in the wake of a host of miscellaneous infections and was diagnosed in 0.2 to 0.5 per cent of the autopsies of large institutions.¹ Bacterial endocarditis was the underlying disease where abscess of the heart originated from local extension of such a process. For a long time, this complication of valvular disease has been considered rare.^{2, 3} Sheldon and Golden,⁴ in 1951, however, applying a meticulous dissection technic, were able to demonstrate abscesses of the valve rings in 12 out of 14 cases of acute bacterial endocarditis (86 per cent). Clinically, this complication is of great importance, considering not only its frequency but also the fact that in all cases the patients had been treated with large doses of penicillin.

We have encountered at autopsy a similar lesion. Also present was a spectacular abscess of the interatrial septum which, clinically, had caused block of the conduction system.

CASE REPORT

A 48-year-old man was admitted to the hospital in November 1950 with the diagnosis of paranoid schizophrenia. No previous medical history was obtainable. On admission, the only abnormal physical finding was a systolic murmur, heard loudest at the apex, with transmission into the left axilla. Blood pressure was 110/68.

In 1952, the heart was found to be enlarged and 2 distinct murmurs were heard at the apex and

the base. Blood pressure then was 132/64. An electrocardiogram in June 1957 revealed no abnormal findings.

In 1958 the patient began to complain of fatigue and progressive weakness. On December 17, 1958, his temperature became elevated to 103 F. Blood pressure was 92/62. Only his lips were cyanotic. In the area of the upper right chest there was a palpable thrill, and a loud, harsh systolic murmur was heard in the second right intercostal space. There were moderate rales in both lungs. The leukocyte count was 31,800. The electrocardiogram revealed complete dissociation of the sinoatrial and ventricular rhythms. A spider-like purpuric macule was noted near the left orbit. Suspecting bacterial endocarditis, we drew blood for culture, and penicillin treatment (2.4 million units intramuscularly and 3 million units intravenously daily) was started. No significant improvement was achieved and he continued spiking fever and chills. The blood culture made prior to antibiotic treatment was sterile as were numerous cultures taken subsequently.

On December 29, 1958, an electrocardiogram showed right ventricular hypertrophy, dissociation of sinoatrial and ventricular rhythms, and atypical right bundle-branch block. Because of an apparent sensitivity reaction to penicillin the antibiotic treatment was discontinued and replaced by salicylates.

On January 3, 1959, the hepatjugular reflex was demonstrable. From January 5 to January 8, 1959, the patient was afebrile.

On January 9, 1959, he developed sudden, acute dyspnea and productive cough. The sputum was foamy and pink, and wet rales and coarse rhonchi were heard in both lungs. Blood pressure soared to 230/80, the pulse rate was 140, and respirations were 48. An electrocardiogram then showed marked changes with total absence of P waves and the suggestion of an intercurrent supraventricular process in comparison to prior tracings.

Despite treatment with oxygen and the usual cardiac regimen, the patient died on January 12, 1959.

At autopsy, 1,200 ml. of clear, straw colored fluid were found in the right and 1,000 ml. in the left pleural cavity. The right and left lungs

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weighed 1,060 and 1,010 Gm., respectively. Their cut surfaces exuded a large amount of fluid.

The heart weighed 630 Gm. It was markedly enlarged in all its chambers, and the apex was formed by the left ventricle. The thickness of the myocardium of the left and right ventricles was 2.1 and 0.5 cm., respectively. The aortic valve was the seat of bulky masses of gray-tan vegetations. The right semilunar valve was completely destroyed. Its crumbly, friable remnants were caked together with the grossly calcified vegetations. There was no encroachment upon the orifices of the coronary arteries. The posterior semilunar valve presented a huge fenestration formed by a bridge of the thickened, free valvular edge (fig. 1). The mitral valve was stenotic, the cusps were thickened and fused, and the chordae tendineae were plump and short (fig. 2) but there was no evidence of active valvular disease. The foramen ovale was closed. Within the interatrial septum, located just anterior and inferior to an unremarkable fossa ovalis, there was a peculiar large swelling that bulged symmetrically into the right as well as into the left atrium, measuring on either side about 4 cm. across. On the right atrial aspect this rounded prominence was covered by intact, glistening endocardium, but just at its vertex there was a 0.5-cm. area of tan-gray and red discoloration with a tiny, gray vegetation in the center. Seen from the left atrial aspect, much of the endocardium covering the prominence in its lower half was similarly discolored, and here a 0.3-cm. defect with ragged edges was noted (fig. 2). A probe was easily introduced to a depth of more than 2 cm. When the swelling was incised from the right atrium, a cavity 3.5 cm. in diameter was entered. It was partly filled with postmortem blood clot. Instead of further routine dissection, the heart was then cut longitudinally in a frontal plane across both venous ostia, thereby dividing the described cavity into an anterior and posterior half (fig. 3). The interior was lined by laminated old thrombus material. It was then found that the cavity anteriorly continued into a short fistulous tract, 0.5 cm. in length, that opened into the sinus of Valsalva of the posterior semilunar aortic valve with the fenestration (fig. 1). The location of this fistulous tract indicates that it traversed and thereby interrupted the annulus fibrosus of the aortic valve.

In the upper pole of the right kidney a 1-cm. area of recent necrosis was found surrounded by a yellow and mottled, dark red, corrugated zone.

The brain weighed 1,370 Gm. The gyri were swollen and flattened. The sulci were narrow. The medullary matter was extremely pale, almost snow white, and pasty. The cerebellar tonsils were prominent.

Microscopically, the pulmonary alveoli contained edema fluid. The mitral valve was fibrotic, with areas of hyalinization. The vegetations of the aortic valve consisted of amorphous eosinophilic masses, areas of calcification, and nuclear debris. Bacterial colonies were not identified. The elements composing the walls of the cavity in the interatrial septum were arranged in an identical fashion on each side. Proceeding from either atrial surface toward the inner lining the following layers were encountered: (1) endocardium, (2) bundles of myocardial fibers, (3) proliferating fibrous tissue, (4) granulation tissue heavily infiltrated with leukocytes, (5) partially organizing thrombus material (fig. 4). Posterior to this cavity, in the thickened interatrial septum, there was an encapsulated abscess filled by leukocytes and nuclear debris, walled in by granulation tissue. In the right kidney there was an area of recent coagulation necrosis surrounded by a hemorrhagic leukocytic demarcation zone.

Final anatomic diagnoses were acute vegetative and ulcerative endocarditis (probably bacterial) of the aortic valve, abscesses of the interatrial septum, with fistula to the sinus of Valsalva of the posterior aortic semilunar valve and rupture into the left atrium, stenosis of the mitral valve due to valvulitis, hypertrophy of the heart, edema of the lungs, pleural effusion, recent infarct of the right kidney, and edema of the brain.

DISCUSSION

The anatomic findings and the clinical course strongly suggest the diagnosis of acute bacterial endocarditis, in spite of the fact that positive blood culture was not obtained. It should be noted, however, that only 1 blood sample was taken for culture before penicillin treatment was started. The absence of bacterial colonies in the vegetations and the areas of calcification indicate that the infectious process of the valves was arrested. The extension of the valvular infection to the annulus fibrosus was followed by the formation of abscesses of the interatrial septum. When the fistula between the large abscess and the sinus of Valsalva of the posterior semilunar aortic valve became established, the interior of the abscess was subjected to the aortic blood pressure and the abscess content was washed out into the general circulation. This, in all probability, happened on December 17, 1958, when the temperature and blood count became significantly elevated. That the interatrial

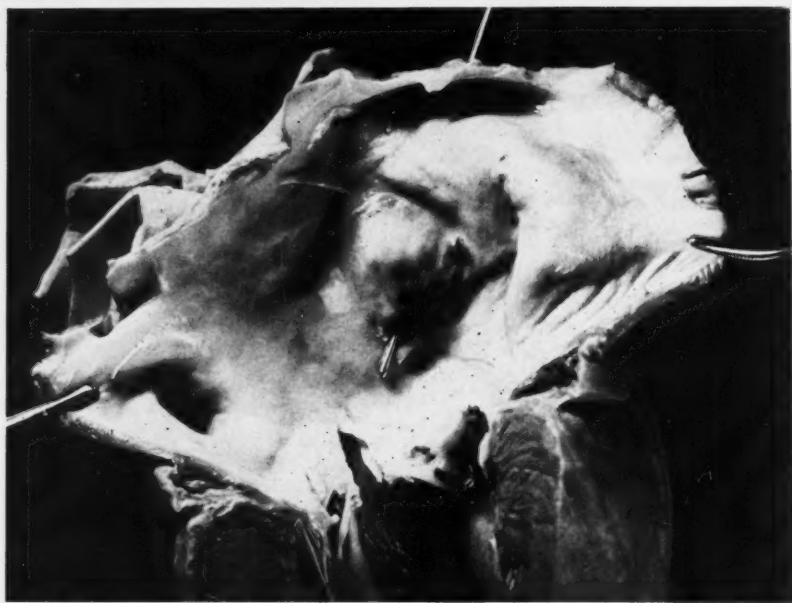
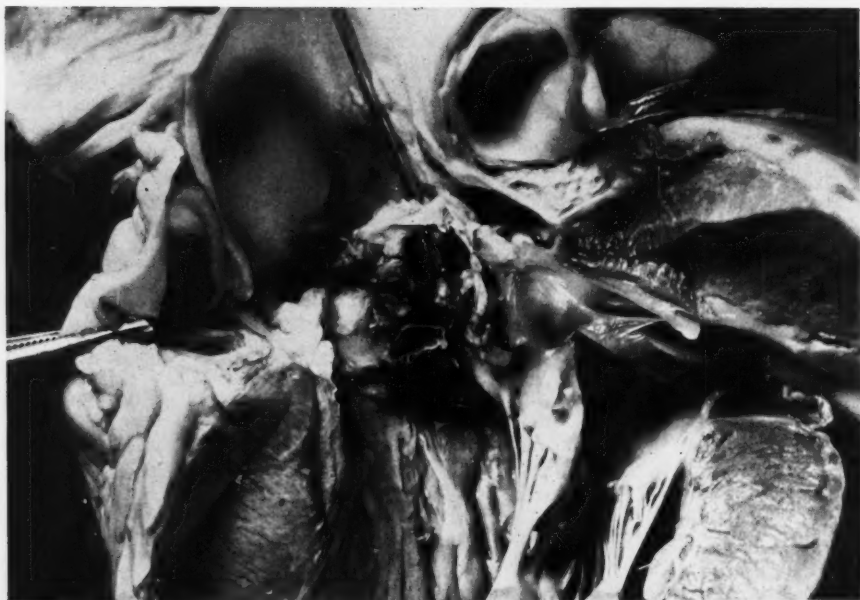


FIG. 1 *Top*. Aortic valve. Bulky vegetations have replaced the completely destroyed right semilunar valve. The posterior semilunar valve is fenestrated. The small dark area just below the tip of the probe marks the opening of the fistula to the interatrial septal abscess.

FIG. 2 *Bottom*. Left atrium. The rounded prominence below the crescent of the valve of the foramen ovale is caused by the underlying abscess of the interatrial septum. The defect marked with the probe leads into the abscess. The probe was introduced from an incision made from the right atrium. The mitral valve is thickened, stenotic, the commissures are fused and the chordae tendineae are short and plump. The split in the mitral valve is an artifact.

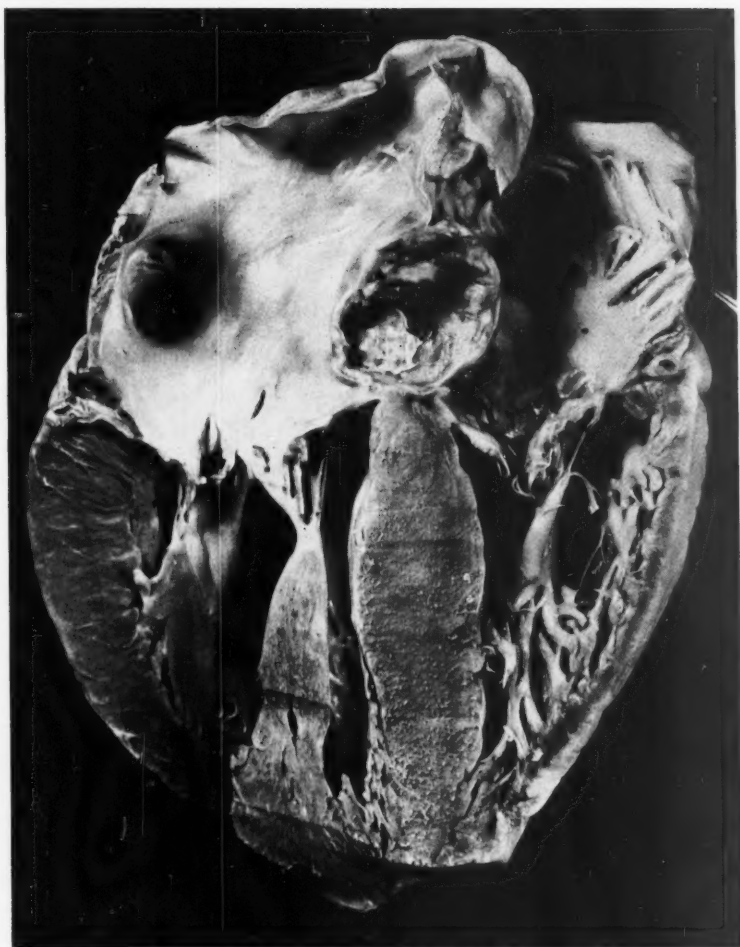


Fig. 5. Photograph of posterior aspect of anterior half of the heart, sectioned longitudinally in a frontal plane across both venous ostia. Note the large abscess cavity in the lower part of the interatrial septum.

septal lesion existed at that time is further evidenced by the dissociation of sinoatrial and ventricular rhythms in the electrocardiogram. Also, the laminated and partly organized thrombus material lining the cavity was at least several weeks old. It is possible, in theory, that the blood burrowed through the valve rings and into the interatrial septum, and that the cavity represented a dissecting aneurysm. This interpretation is excluded by the presence of granulation tissue in the cavity wall. Secondly, a separate, closed abscess was also found in the interatrial septum.

It would appear that the sudden and drastic onset of dyspnea, pulmonary edema, and hypertension on January 9 marks the time of rupture of the cavity into the left atrium. Then, blood must have flowed from the aorta through the fistula into the abscess and from there into the left atrium. The site of rupture was a small defect with thin and ragged edges, which appeared fresh, and was certainly not older than a few days. It seems reasonable to speculate that the rupture effected a pressure release in the cavity at this point, the electrocardiographic interpretation

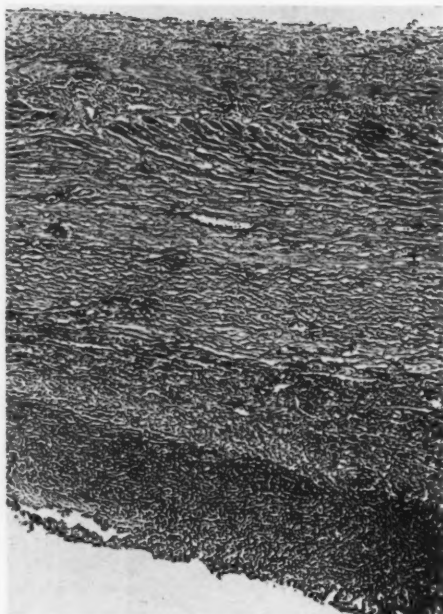


Fig. 4. Photomicrograph of the wall of the interatrial septal abscess. From the top to bottom the following layers are encountered: (1) atrial endocardium, (2) bundles of myocardial fibers, (3) proliferating fibrous tissue, (4) granulation tissue heavily infiltrated by leukocytes, magnification, and (5) organizing thrombus material. $\times 50$.

was that of total absence of P waves and the suggestion of an intercurrent supraventricular process in comparison to prior tracings.

Some authors^{4, 5} have expressed the opinion that the incidence of cardiac abscess following bacterial endocarditis has increased with penicillin treatment. We are rather inclined to attribute the large number of abscesses found by Sheldon and Golden to their careful and unusual dissection technic (step section of the valve rings).

SUMMARY

Abscess of the heart due to bacterial endocarditis appears to be more frequent than was thought in the past. A case is presented in which acute endocarditis was followed by a spectacular abscess of the interatrial septum. This lesion was complicated by a fistula and rupture, connecting the abscess with the aorta and the left atrium as well.

The mechanics of this incidence and their reflection in the patient's clinical course are discussed.

The high proportion of cardiac abscesses complicating bacterial endocarditis, as demonstrated by some authors, may be related to their dissection technic especially designed for the finding of such lesions.

ACKNOWLEDGMENT

The authors wish to thank Dr. Chester B. Allen Jr., of Upper Montclair, N. J., for assistance in interpreting the electrocardiograms.

SUMMARY IN INTERLINGUA

Abscesso del corde como effecto de endocarditis bacterial es apparentemente plus frequente que lo que esseva credite in le passato. Es presentate un caso in que endocarditis acute esseva sequite per un abscesso spectacular del septo interatrial. Iste lesion esseva complicate per un fistula con ruptura que connecteva le abscesso con le aorta e etiam con le atrio sinistre.

Le mechanica de iste typo de occurrentia e su effecto super le curso clinic del patiente es discutate.

Le alte proportion de abscessos cardiac complicante endocarditis bacterial secundo le reportos de certe autores es possibilmente relationate a lor technica de dissection que es specialmente orientate verso le detection de tal lesiones.

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SPECIAL ARTICLE

Effects of Carotid Sinus Reflex on Cardiac Impulse Formation and Conduction

By ARTHUR J. LINENTHAL

REFLEXES arising from stimulation of pressor receptors in the carotid sinus produce marked effects on the heart, on the blood pressure, and on the brain. Various aspects of these reflexes have been extensively described by others.¹⁻³ This report is concerned primarily with the effects of carotid sinus stimulation on cardiac impulse formation and conduction in man: the anatomy, physiology, and pharmacology of the reflex, and the clinical significance of these potent cardiac effects.

Anatomy

The carotid sinuses, slight bulbar enlargements of the internal carotid arteries at the bifurcation of the common carotid arteries, contain receptors that are stimulated by stretching of the sinus wall brought about by pressure changes in the vessel.³ Pressor receptors are also present in the walls of the common, internal, and external carotid arteries for a short distance above and below the sinuses. Afferent impulses from the carotid sinus are transmitted to the brain stem over the carotid sinus and glossopharyngeal nerves. Efferent impulses to the heart are transmitted over vagal pathways. Within the heart post-ganglionic parasympathetic fibers are distributed to the sinoatrial node, the atria, and the atrioventricular node; there appears to be no parasympathetic innervation of the ventricles.

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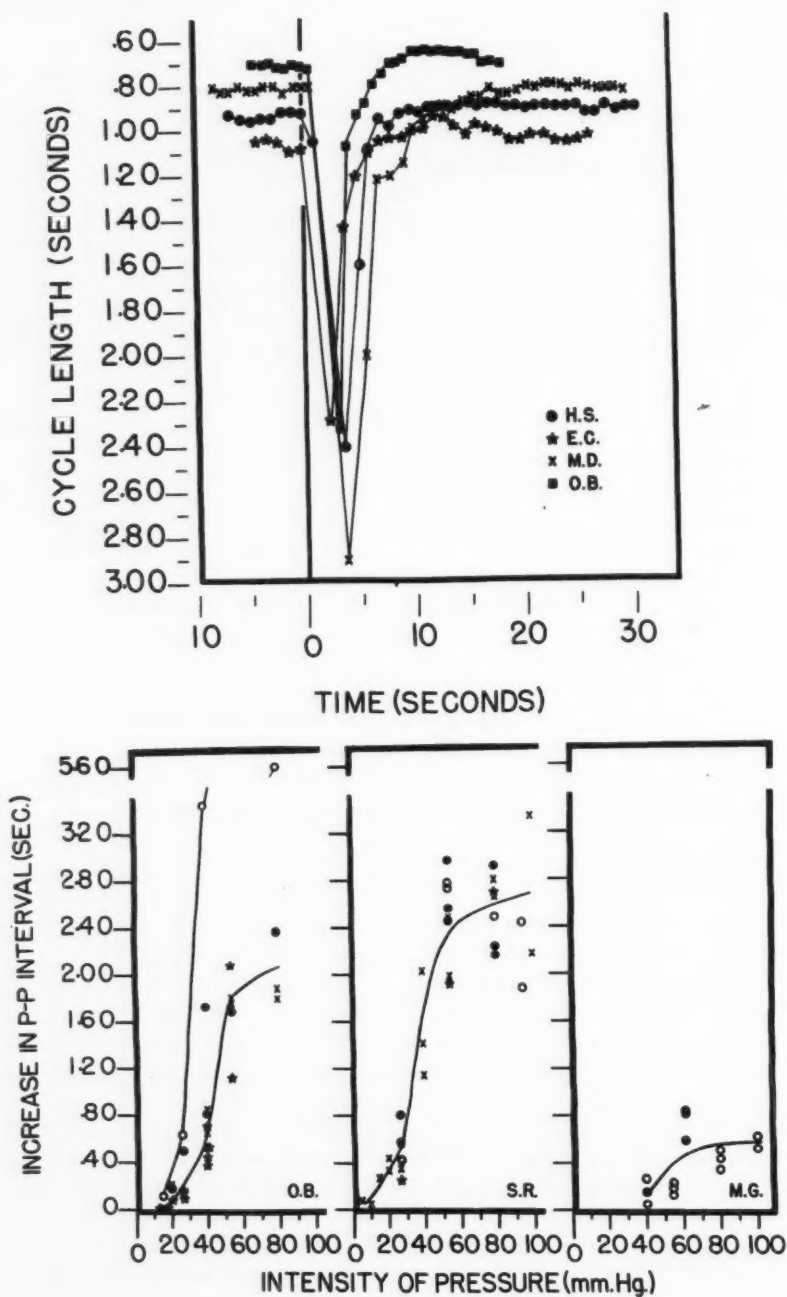
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In the brain, impulses may also go to the vasomotor center and to the cerebral vessels.

Physiology

Carotid sinus pressure may cause systemic vasodilatation and cerebral vasoconstriction as well as a variety of cardiac effects. The changes in cardiac impulse formation and conduction are due to simultaneous vagal stimulation and sympathetic inhibition during pressure, and to sympathetic rebound stimulation after pressure is released. As shown by the magnitude of the maximum cardiac effects, the activity of the carotid sinus cardiac reflex varies greatly in different people. In general, the effects are greater in older individuals, particularly those with hypertension or coronary artery disease. The segment of the reflex arc responsible for hyperactivity of the reflex has been established in a patient with angina pectoris:⁴ the increased effect was localized either in the intrinsic cardiac nerves to the atrioventricular node or in the node itself. Less commonly, hyperactivity of the reflex may be associated with lesions of the carotid sinus (such as aneurysm or tumor), or with central nervous system lesions (such as tumor or syphilis).

Studies in our laboratory with a technic of controlled, measured pressure on the carotid sinus have provided a quantitative analysis of various aspects of these effects on cardiac impulse formation and conduction in man. During normal sinus rhythm the most common reflex vagal effect on the heart is a negative chronotropic one, the production of a slower sinoatrial rate, manifested electrocar-



FIGS. 1 and 2. (See legends on opposite page.)

biographically by prolongation of the P-P interval. This effect may occur with either right or left carotid sinus pressure. In different individuals the amount of maximum slowing may vary markedly; it may be so slight as to be detected only by electrocardiographic measurements or it may be manifested by cardiac asystole lasting up to 10 seconds and associated with cerebral ischemia and syncope. When pressure on the carotid sinus is raised instantly to an effective level and is maintained at this level for 3 seconds, the maximum prolongation of the P-P interval is often observed in the first cardiac cycle and routinely occurs by the end of pressure (fig. 1). When pressure is discontinued, the sinoatrial rate returns to its control level within 6 to 7 seconds and may then show a slight, brief acceleration. The time to reach the maximum effect and the time for the effect to disappear do not depend on the magnitude of the slowing or on the sinoatrial rate before pressure is applied.

When constant pressure is applied for 30 seconds or more, the sinoatrial rate often returns to its control level within 10 to 15 seconds after the beginning of pressure. Occasionally some vagal effect may persist for at least several minutes with continued application of pressure.

The relation between the intensity of the pressure and the magnitude of the sinoatrial slowing is shown in figure 2. With only a slight increase in pressure above the threshold, the effect increases quickly to a nearly maximum degree and then tends to level off. The variation in the response among different individuals and between the right and left carotid sinuses in the same individual (O.B.) is apparent in these data.

A second, less common reflex vagal effect on the heart during normal sinus rhythm is interference with atrioventricular conduction, shown in the electrocardiogram by prolonged P-R intervals, nonconducted (dropped) sinoatrial beats, varying degrees of partial heart block, or complete atrioventricular block. Complete heart block is usually followed within a few seconds by the appearance of idioventricular beats; occasionally ventricular standstill may persist long enough to produce symptoms of cerebral anoxia (faintness, dizziness, syncope, convulsions). Many features of this effect on conduction are similar to those of the sinoatrial slowing: it may occur with either right or left carotid sinus pressure, and its appearance and disappearance follow a pattern similar to that of the slowing. Although these 2 effects often occur at the same time, they are quite independent. Prolongation of the P-P interval usually occurs with less intense pressure than is required to prolong the P-R interval. In certain individuals, however, marked prolongation of the P-R interval and even dropped beats may occur with little change in the sinoatrial rate.

Other changes in sinoatrial rhythm produced by carotid sinus pressure are related to its varying action on other cardiac pacemakers as well as on the sinoatrial node. For example, a greater vagal depression of the sinoatrial node as compared with lower pacemakers may permit the escape of an atrioventricular nodal rhythm or an idioventricular rhythm during sinoatrial slowing. After the end of pressure, on the other hand, when the vagal influences have disappeared, rebound increased activity of the previously inhibited sympathetic stimuli may excite the sinoatrial node less than it does other centers, resulting

Fig. 1 *Top*. Changes in sinoatrial cycle length produced by carotid sinus pressures of 3 seconds' duration. Observations were made in 4 patients with coronary artery disease. Zero time indicates the start of pressure.

Fig. 2 *Bottom*. Relation between the intensity of carotid sinus pressure and the sinoatrial slowing. Observations were made in 3 patients with coronary artery disease. *Points* indicate maximum increase in P-P interval produced by a single application of pressure. For patient O.B. the lower curve represents pressure applied to the left carotid sinus on 3 days, the upper curve pressures applied to the right carotid sinus on 1 day. Observations on 5 days are recorded for patient S.R., and on 2 days for patient M.G.

in extrasystoles or runs of atrial, atrioventricular nodal, or ventricular tachycardia.

Carotid sinus pressure may also markedly affect the heart during various cardiac arrhythmias. The rapid ectopic impulse formation of paroxysmal atrial tachycardia or paroxysmal atrioventricular nodal tachycardia may be stopped abruptly and sinoatrial control may be restored. Ventricular tachycardia, on the other hand, is not affected. During atrioventricular nodal rhythm associated with absent sinoatrial activity, carotid sinus pressure may slow the atrioventricular nodal rate and may lead to an idioventricular rhythm.

In addition to these effects on abnormal types of impulse formation, carotid sinus pressure applied during partial atrioventricular or ventriculoatrial block may cause an increase in the conduction defect. Although reflex vagal stimulation has no effect on the ectopic impulse formation in atrial fibrillation or atrial flutter, it may increase the degree of block and thereby slow the ventricular rate. In contrast to this depressing action of carotid sinus pressure on atrioventricular conduction, in some patients with transient left bundle-branch block reflex vagal stimulation may temporarily restore normal intraventricular conduction without changing the rate.⁵ Another effect of carotid sinus pressure on atrioventricular conduction is seen in the production of anomalous atrioventricular conduction (Wolff-Parkinson-White syndrome) in susceptible individuals.

Pharmacology

Various commonly used drugs may influence the cardiac effects of carotid sinus pressure. Vagomimetic drugs such as acetyl-beta-methylcholine and neostigmine, digitalis glycosides, and veratrum alkaloids may all potentiate these effects. Previously ineffective pressure on the carotid sinus may produce marked cardiac effects when reapplied following the administration of one of these agents. Even sympathomimetic drugs, by their vasoconstrictor action, may stimulate pressor recep-

tors and produce reflex vagal effects on the heart.

On the other hand, vagolytic drugs such as atropine, and sympathomimetic agents such as epinephrine, ephedrine, and phenylephrine may decrease or block completely the carotid sinus cardiac reflex. This blocking effect may not be the same on all parts of the cardiac impulse-forming and conducting system. Atropine, for example, in submaximal doses may interfere with a reflex vagal depression of the atrioventricular node without altering the effect on the sinoatrial node. Under these circumstances carotid sinus pressure which previously produced only slight sinoatrial slowing without a shift in the pacemaker after atropine may slow the sinus node similarly and also lead to atrioventricular nodal rhythm. Drugs such as epinephrine and ephedrine may have a 2-fold action: they may counteract the depressing effect of reflex vagal stimulation on the sinoatrial node and they may stimulate the more prompt escape of lower pacemakers. In experimental animals quinidine also has been found to block the cardiac effects of direct electric stimulation of the vagus nerves; a similar effect in man probably occurs only with very large doses. Procaine hydrochloride injected into the wall of the carotid sinus or infiltrated around the nerves from the carotid sinus will temporarily block the reflex activity.

CLINICAL APPLICATIONS

Carotid sinus pressure is of clinical value principally in the diagnosis and treatment of certain cardiac arrhythmias and in the diagnosis of the carotid sinus syndrome.

Digital pressure on the carotid sinus is performed with the patient either supine or in a semirecumbent position and with the head slightly rotated away from the side to be stimulated. The carotid sinus can often be felt as an expansile mass situated below the angle of the jaw usually at the level of the thyroid cartilage. Frequently it is impossible to feel the actual bulbous enlargement and one must be guided by the point of maximum

carotid pulsation. The greatest difficulty is experienced in patients with short, thick necks. Pressure is applied toward the vertebral column by rubbing vigorously with several fingers over the carotid sinus and several centimeters above and below. It is important to retract the carotid artery laterally to prevent the vessel from slipping medially. When pressure on either carotid sinus alone is ineffective; both carotid sinuses may be gently pressed simultaneously. In its clinical uses effective carotid sinus pressure need not be applied for more than a few seconds and ineffective pressure should not be applied for more than 10 seconds.

During application of carotid sinus pressure the physician should observe the cardiac activity by listening to the heart beat or by watching the electrocardiogram. Transient dizziness or lightheadedness occasionally occurs when there is no ventricular beat for 2 or 3 seconds. Excessive cardiac effects which may lead to syncope and convulsions must be avoided by stopping the pressure when the first definite effect is observed. Rarely, complete atrioventricular block and ventricular standstill may persist following carotid sinus pressure, especially in patients with Stokes-Adams disease who are subject to spontaneous attacks of ventricular standstill. External stimulation of the heart by slapping the precordium or with an electric pacemaker is useful in such circumstances to terminate the standstill and to resuscitate the patient.

Untoward effects of carotid sinus stimulation most commonly occur when the pressure is prolonged and intense, when it is applied with the patient in the sitting or standing positions, when it is applied to both carotid sinuses simultaneously, or when the patient is elderly. In older patients with generalized arteriosclerosis, carotid sinus pressure of excessive duration with complete occlusion of the carotid artery has been followed by transient or permanent hemiplegia. Syncope and convulsions can also occur in the absence of significant cardiac slowing, as a result of a direct effect on the brain. Pressure on the

carotid sinus may also stimulate reflexes to the coronary arteries, to other major vessels, to the bronchial smooth muscle, and to the gastrointestinal tract; resulting manifestations may include precordial pain, hypotensive symptoms, wheezing, and gastrointestinal symptoms.

Diagnosis of Cardiac Arrhythmias. Changes in cardiac impulse conduction as a result of carotid sinus pressure may be helpful in the diagnosis of certain cardiac arrhythmias. The precise electrocardiographic recognition of a supraventricular arrhythmia, for example, may be difficult when the P waves are obscured by rapid ventricular complexes. Carotid sinus pressure, by interfering with atrioventricular conduction, may slow the ventricular rate enough to reveal the electrocardiographic configuration of the supraventricular activity. This effect is most often useful in the diagnosis of atrial flutter with 2:1 block and may also be helpful in paroxysmal atrial tachycardia with 2:1 block. The marked, irregular ventricular slowing which occurs with carotid sinus pressure and disappears at once when pressure is stopped is so characteristic of atrial flutter that it can be used at the bedside to differentiate this arrhythmia from other rapid, regular tachycardias.

Because of its effect on cardiac impulse formation and conduction, carotid sinus pressure may be useful in the analysis of complex arrhythmias. For example, transient slowing of a dominant supraventricular pacemaker may reveal a ventricular parasystolic focus, and prolongation of ventriculoatrial conduction may demonstrate retrograde conduction as the mechanism of coupled beats.

Treatment of Cardiac Arrhythmias. Carotid sinus pressure often terminates paroxysmal atrial tachycardia and paroxysmal atrioventricular nodal tachycardia. This simple procedure can be carried out by the patient himself as well as by the doctor and, if effective, may be extremely valuable when attacks recur frequently and drug prophylaxis is unsuccessful. There is no necessary relation

between preexisting hyperactivity of the carotid sinus reflex and the efficacy of carotid sinus pressure in stopping an episode of tachycardia. The effect usually consists of an immediate restoration of sinoatrial rhythm, occasionally with very slight preliminary slowing of the ectopic pacemaker. Rarely is there significant slowing of the arrhythmia if normal sinus control is not restored. Once normal sinus rhythm returns usually it persists, although occasionally it may be transient and carotid sinus pressure may need to be repeated.

The simplicity and safety of carotid sinus pressure make it the initial procedure of choice to be tried in all cases of paroxysmal supraventricular tachycardia. The absence of an effect does not exclude the possibility of an active response to another means of producing reflex vagal stimulation, such as pressing on the eyeballs, inducing vomiting, breathing deeply, expiring forcibly against the closed glottis after a deep inspiration (Valsalva maneuver), and swallowing a large bolus. Failure of these measures at one time during an episode of tachycardia does not preclude success later in the same attack; accordingly, they should be tried repeatedly before resort to other forms of therapy. If a vagomimetic drug or a digitalis glycoside is administered, previously ineffective reflex maneuvers should be repeated, since they may then be effective.

Diagnosis of the Carotid Sinus Syndrome.

An occasional person with a hyperactive carotid sinus reflex may develop the carotid sinus syndrome; that is, spontaneous symptoms occur as a result of stimulation of the carotid sinus by such means as a tight collar, pressure from shaving, or turning the head. The symptoms may include dizziness, faintness, paresthesias, syncope, and convulsions; most often they are due to marked cardiac slowing, but they may also result from a drop in blood pressure without change in the heart rate, or from a reflex effect directly on the brain. Treatment may consist of specific drugs such as atropine or ephedrine, surgical

denervation of the carotid sinuses, or irradiation of the carotid sinus area.

The diagnosis of this syndrome depends upon repeated, exact reproduction of the spontaneous symptoms by manual pressure on the carotid sinus. A careful analysis of each suspected case is essential, since many individuals who have symptoms from pressure on the carotid sinus do not have spontaneous symptoms, and a hyperactive carotid sinus reflex may be present along with some other disturbance causing cerebral symptoms. Conditions such as epilepsy, hypoglycemia, postural hypotension, and vasovagal syncope must be differentiated.

In patients with Stokes-Adams disease, attacks of syncope due to ventricular standstill may be precipitated by spontaneous stimulation of the carotid sinus. Diagnostic carotid sinus pressure should be applied with great care in such patients and with an external cardiac pacemaker at hand, since, if ventricular standstill occurs, it may last long enough to cause severe cerebral symptoms.

Diagnosis of Acute Myocardial Infarction during Left Bundle-Branch Block. The electrocardiographic diagnosis of acute myocardial infarction may be difficult in the presence of left bundle-branch block. In certain individuals with left bundle-branch block carotid sinus pressure may paradoxically restore normal intraventricular conduction. If the block can thus be temporarily abolished, the electrocardiographic changes of acute myocardial infarction may become apparent. Carotid sinus pressure should be applied cautiously in patients with acute myocardial infarction, since the cardio-inhibitory reflex may be quite active.

Miscellaneous Cardiovascular Effects. Carotid sinus pressure has been found to be effective occasionally in terminating attacks of angina pectoris. This effect is independent of any action on the heart rate and has been attributed to an interruption of sympathetic reflex arcs or sensory pathways.⁶ The relief of pain is not known to be specific for cardiac pain and some patients with angina pectoris

not helped. Accordingly, and in view of the hazards involved, carotid sinus stimulation is not considered to be clinically useful in the diagnosis or treatment of angina pectoris.

Carotid sinus pressure has also been found to terminate attacks of acute pulmonary edema in certain hypertensive patients.⁷ Prolonged application of pressure is described and this is undoubtedly hazardous. As in the case of anginal attacks it seems likely that this effect is independent of any action on the heart rate.

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BEING TRUE TO ONE'S CONVICTIONS

THOMAS H. HUXLEY

English biologist, 1825-1895

Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatever abysses nature leads, or you shall learn nothing. I have only begun to learn content and peace of mind since I have resolved at all risks to do this.—*Life and Letters of Thomas H. Huxley*. From *Great Companions*. *Readings on the Meaning and Conduct of Life from Ancient and Modern Sources*.

SPECIAL ARTICLE

Approach to Diagnosis of Congenital Heart Disease without Recourse to Special Tests

By ALEXANDER S. NADAS, M.D.

THE title of my presentation of course, raises the question: What is a special test? I would think that I am expected to discuss procedures customarily performed in the office *today*. One can take a good history and do a good physical examination. One can take x-rays, do fluoroscopies, and electrocardiograms.

The next point I would like to raise concerns the use of some of these office tools such as the stethoscope. I would like to put in a word that you should use a stethoscope of the proper length (10 inches), with proper tubing (1/8-inch bore), equipped with 2 end-pieces, a diaphragm, and an open bell.¹ I also must tell you that I have found surprising improvement in the accuracy of my auscultation by doing the very complicated maneuver of cleaning out the ear pieces.

Next I would like to make a few remarks about a second tool, the fluoroscope. Fluoroscopy can teach us a lot, but it involves a great deal of radiation, relatively speaking. My radiologist friends tell me that a *minute* of fluoroscopy under ideal circumstances, generates about 6 r's, whereas only .25 r is involved in a posteroanterior film of the chest.² So I would like to caution you to use fluoroscopy sparingly. In our hospital we fluoroscope all patients initially, and then no more often than once every 2 to 3 years, and in the majority, even less frequently, when specific reasons arise. We rather prefer to

gauge the progress of the patient with 7-foot posteroanterior films, and possibly oblique views. Our radiologists think, and I know that not everybody agrees, that the pulmonary vasculature may actually be judged better by films than by fluoroscopy. This, then, is an added reason for the use of films.

As far as electrocardiography is concerned, I don't think I have to spend time on general advice. I would like to say only that if you are dealing with children, please don't be satisfied with the usual V_1 to V_6 leads, but take V_{4R} , maybe V_{3R} , and leads above or below V_{4R} , so that you get a complete R/S progression from a dominant complex on one side of the chest to a dominant complex on the other. We have been using vectorcardiography to a certain extent within the past year, and it is proving to be a fairly useful addition, giving information not obtainable by the conventional scalar leads in certain specific instances.

Now once we are equipped with all these tools, I would like to ask, "What is really the role of the clinician in evaluating congenital heart disease?" The first question I have to answer when I am confronted with a child—this being 90 per cent of my experience—is, does he have heart disease, or not? This is very important, since we are all confronted in our daily practice by a number of children referred with a tentative diagnosis of heart disease, who, on the basis of a thorough office examination may be pronounced healthy. I would like to propose certain criteria for the diagnosis of heart disease in children.

I would like to use the type of classification that Dr. T. Duckett Jones used for rheumatic

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fever,³ and say that there are certain major and minor criteria. By major criteria I mean, for the purposes of this discussion, that the presence of any one of them should enable the clinician to make the diagnosis of heart disease (table 1). The first thing, of course, is a systolic murmur more than grade III in intensity. If this is accompanied by a thrill, then the diagnosis of heart disease can be even more certain; but even without a thrill, a grade III (on a scale of I to VI)⁴ systolic murmur is usually adequate evidence on which to base the diagnosis of heart disease.

The second major criterion is a diastolic murmur of any intensity. This alone is proof positive, in the vast majority of instances, to establish the diagnosis of heart disease.

The third point is congestive heart failure. This, even in the absence of a murmur, proves the presence of heart disease. Of course, one has to look out for pitfalls, and I hasten to assure this group that we have fallen into these ourselves, just as much as anybody else in this audience. We have had a patient with "nephrosis" sitting on our ward for a month before right-sided congestive failure was recognized. We also have had small babies with "asthma," who, on investigation, turned out to have left-sided failure. On the whole, however, signs or symptoms of left or right-sided failure, per se, are enough to establish the diagnosis of heart disease.

The final major criterion is cyanosis. Again, you have to watch out for pitfalls. Abnormal hemoglobins, pulmonary disease, well-water methemoglobinemia and all the other things one tortures medical students with at examination time ought to be thought of, and usually discarded. If you can be sure that the cyanosis is indeed cardiac in origin, you may make a diagnosis of heart disease with assurance.

The second group of criteria, the minor ones, are those of which 2 are needed for a certain diagnosis of heart disease. Among them is a systolic murmur less than grade III in intensity. These are the faint murmurs, and many may be classified as innocent. Some-

TABLE 1.—Criteria for Diagnosis of Heart Disease

Major 1	Minor 2
Systolic murmur > III	Systolic murmur < III
Diastolic murmur	Abnormal x-ray
Congestive heart failure	Abnormal electrocardiogram
Cyanosis	Abnormal blood pressure
	Abnormal S ₂

thing else such as an abnormal electrocardiogram or x-ray must go with it before the diagnosis of heart disease can be established.

But an abnormal electrocardiogram alone is again probably insufficient evidence to make the diagnosis of heart disease. Within the framework of coronary disease, this may not be true; but in children, I think the electrocardiogram, although we have good standards for normal, is by itself probably not enough to establish the diagnosis of heart disease. On the other hand, if you couple the electrocardiogram with another criterion, it becomes decisive.

Abnormal x-rays may give us a great deal of trouble, particularly in small babies with a large thymus. They may have large mid-thoracic shadows. The parents live in fear and trepidation for months, saying, "This child has heart disease." In fact, the heart may be normal, but the thymus is large. Another pitfall in this regard is the difference in heart size between inspiration and expiration films; I am sure this is known to everybody. Still it may be well worthwhile to stress this point in order to reinforce the principle not to accept an abnormal x-ray without other criteria as convincing evidence of heart disease.

I would also like to say a few words about the abnormality of the second sound at the second left interspace. Sometimes the degree of the splitting, or the intensity of the second sound, may be a very important clue to lead you to recognize or discard heart disease. A widely split second sound, particularly if it does not change with respiration, suggests an atrial septal defect. A markedly accentuated pulmonary closure indicates pulmonary hypertension. A diminished second sound means,

usually, low mean pulmonary arterial pressure.

The final criterion is the abnormality of blood pressure, particularly the relative hypertension of the upper extremities characteristic of coarctation of the aorta. This may be used almost as a major criterion, but I doubt that you will find it without the appearance of murmur or abnormality of the electrocardiogram or x-ray.

Once we have established the diagnosis of heart disease on any basis, the next point is, "Is this congenital or is it acquired?" In children I think this is fairly easy. Obviously there is the time factor. Although people talk about rheumatic heart disease appearing congenitally, or within the first year of life, I believe that this is quite rare in the experience of those who see many patients with rheumatic heart disease. If a patient has a murmur or other evidences of heart disease under the age of 1, or even under the age of 2, you may assume that it is congenital in nature.

It should be emphasized, however, that the late discovery of a murmur is not necessarily evidence *against* congenital heart disease. There are certain types of congenital cardiac defects, particularly ostium secundum atrial septal defect, in which murmurs are particularly prone to appear or to be discovered late. The murmurs of an atrial septal defect are commonly discovered for the first time during an examination for entering school. Coarctation of the aorta, with the relative hypertension of the upper extremities and the murmur over the back, is just as commonly discovered when the child is 10 or 12 years old. Finally, although a patent ductus arteriosus is discovered quite often in infancy, we see a surprising number of youngsters who have had good pediatric care in whom the characteristic Gibson murmur does not appear, or is not discovered, until 3 or 4 years of age.

It may be worthwhile to contrast the conditions in which murmurs usually appear early in life. Foremost among these are aortic ste-

nosis, pulmonic stenosis, and ventricular defect.

In addition to time factors, the presence of cyanosis means congenital heart disease for all practical purposes. Then there is the location of the murmur. Parasternal systolic murmurs suggest congenital disease strongly. Conversely, apical murmurs do not mean rheumatic heart disease, necessarily; many congenital conditions manifest themselves by a loud murmur at the apex.

If on the basis of the foregoing principles one has established the diagnosis of congenital heart disease, we may turn our thoughts toward one or another specific entity with the aid of certain group characteristics.

The first large group to think of is the group of so-called left-to-right shunts. In these patients there is a communication between the systemic and pulmonary circuit anywhere from the patent ductus down to the atrial level, including pulmonary venous anomalies. The group characteristics of the left-to-right shunts include (1) pulmonary vascular engorgement by x-ray; (2) hyperkinetic cardiac impulse; (3) left-sided chest prominence; (4) lower left sternal border, or apical protodiastolic, so-called "shunt," rumble; and (5) absence of cyanosis. If the diastolic rumble is loud, if the pulmonary vasculature is not only engorged, but also shows expansile pulsations, and if the cardiac silhouette is appreciably enlarged, one may assume that the shunt is of considerable magnitude.

The next big group to be considered is the groups of right-to-left shunt. These are the patients with cyanosis and clubbing. Occasionally, these 2 features may not be present in equal degree. The cyanosis may be minimal, or may only be represented by an intense redness of the toes and fingers, but the clubbing may be marked. This large group of cyanotic patients may be subdivided into those (a) associated with pulmonary stenosis (stenotic, systolic murmur at the second left interspace, diminished pulmonary closure, and ischemic lung fields); (b) those with pulmonary vascular obstruction (pulmonary pl-

tora, loud pulmonary closure, and slight systolic murmur); and finally (c) the transpositions (underdevelopment, pulmonary plethora, and absent main pulmonary artery at the usual place).

Finally, the third large group of congenital heart diseases are the obstructive lesions without shunts, such as coarctation of the aorta, aortic stenosis, and pulmonic stenosis. These patients, as a group, are characterized by a diamond-shaped stenotic, systolic murmur often accompanied by a thrill. The cardiac impulse, in contrast to the left-to-right shunt group, is heaving. The presence of chest deformity is relatively rare, and diastolic rumbles are usually absent or faint. Cyanosis is of course not present.

Once one has classified the patient into one of these large groups, then on the basis of individual features, an accurate diagnosis may be rather easily made. For instance, in the obstructive group, if the murmur is loudest over the back, one probably is dealing with a coarctation of the aorta. If it is best heard at the second left interspace, it is probably pulmonic stenosis, whereas with aortic stenosis the same type of murmur is heard to the right of the sternum. Within the left-to-right shunt group, in a similar fashion, a secundum-type atrial defect may be recognized by the wide and fixed splitting of the second sound, and a soft, ejection-type systolic murmur at the second left interspace. By contrast, an endocardial cushion defect is identified by a mean electrical axis of between -20 to -180° , and a ventricular defect is recognizable by a harsh, systolic murmur at the lower left sternal border. Of course, the ductus can easily be

identified by a continuous machinery murmur.

All of this, of course, is not simple, and particularly the cyanotic group may be extremely complicated. I still believe, however, that with the intelligent use of the eyes, ears, and hands, the electrocardiogram, and the x-rays, the diagnosis of congenital heart disease may be made with relative ease in about 75 per cent of the cases. I also think that probably about one third of the remaining 25 per cent cannot be accurately diagnosed by any means short of an autopsy.

All of this does *not* lead me to say not to use all the tools available for accurate anatomic and physiologic diagnosis necessary to give a maximal amount of information for the surgeon; but I do mean that with an intelligent use of the clinical tools, one can direct the physiologic studies into the more fruitful avenues, and may gradually arrive at the point where a good number of these lesions can actually be accurately analyzed without the use of more complicated, cumbersome, and expensive methods.

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CLINICAL PROGRESS

Diagnosis of Diffuse Myocardial Fibrosis

By C. SIDNEY BURWELL, M.D., AND EUGENE D. ROBIN, M.D.

SIXTY-EIGHT patients with constrictive pericarditis were studied by this laboratory in a 30-year period. During this time 14 patients were encountered whose findings suggested constrictive pericarditis but who showed an abnormal myocardium at operation or autopsy. Two of these patients had both constrictive pericarditis and myocardial fibrosis, each of the other 12 had a normal pericardium. The hemodynamic aspects of diffuse myocardial fibrosis as exemplified in 10 of these patients have been described by Robin and Burwell.^{1,2}

The purpose of this paper is to describe the course and manifestations of diffuse myocardial fibrosis in these 14 patients, to discuss the diagnosis of this disorder, and to consider the differentiation of myocardial fibrosis from constrictive pericarditis. The fact that constrictive pericarditis is to some degree remedial by surgery makes this differentiation of high importance.

Myocardial fibrosis is defined as a diffuse replacement or invasion of the myocardium by fibrous connective tissue to such an extent that there is interference with the action of the heart. It may be expected that the nature, location, and extent of such fibrosis will influence its manifestations in a given patient.

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Such fibrosis can result from a number of causes. Probably the most frequent cause is coronary artery disease, but many other diseases involving the myocardium diffusely can also result in myocardial fibrosis. Some such causes are listed in table 1. Diversity of cause is also true of constrictive pericarditis; a number of etiologic agents produce inflammation of the pericardium that may result in the ultimate development of restrictive disease of the heart.

We present now brief summaries of the course and manifestations of diffuse myocardial fibrosis in our 14 patients. Ten of these patients were studied by right heart catheterization and the results were published in detail.¹ In the present paper only general statements are made about this aspect of the diagnostic observations.

CASE REPORTS

1. *W.L. PBBH 7A331*. This patient was a 38-year-old streetcar conductor who entered the hospital because of severe and disabling dyspnea. At the onset of his disability 5 years earlier he was treated at another hospital for what was called "influenza and pneumonia" and was given digitalis. Shortly after his discharge, shortness of breath and swelling of the abdomen recurred. From this time he was severely incapacitated in spite of continued administration of digitalis, restriction of sodium in the diet, and weekly injections of diuretics. At no time did he have chest pain suggesting coronary artery insufficiency.

On physical examination he looked pinched and thin. The neck veins were distended and pulsating. Venous pressure was 320 mm. of water. The arterial blood pressure was 115/80; cardiac enlargement was evident; cardiac rhythm was regular; no murmurs were audible but the pulmonic second

sound was accentuated. Over the bases of the lungs there were persistent rales. The liver was enlarged, and the physical signs of ascites were present. Pitting edema of the lower extremities was observed.

The electrocardiogram was interpreted as indicating right axis deviation. The vital capacity was 1400 ml. and the circulation time (Decholin) was 27 seconds. X-ray examination showed a large heart without evidence of calcification. The excursions of the cardiac border as observed under the fluoroscope were interpreted as abnormally small.

Cardiac catheterization showed a low cardiac output per minute and per beat and a "plateau of pressures" at the level of approximately 40 mm. Hg. This plateau extended from the "pulmonary capillaries" to the peripheral veins. Pressure tracings from the right atrium showed an "M" form and from the right ventricle a diastolic "dip."

Because constrictive pericarditis was considered a real possibility, a thoracotomy was performed. This revealed a pericardium of normal appearance. Eight months later, the patient died and post-mortem examination showed gross occlusion of all 3 main coronary arteries by atherosclerosis. There was evidence of multiple myocardial infarctions, both old and recent. Microscopic study revealed extensive, diffuse myocardial fibrosis and a normal pericardium.

2. *L.H. PBBH 7E92.* This patient was a housewife aged 39 years who entered the hospital because of shortness of breath. She reported that 7 years before she had been admitted to another hospital because of rapid heart action. She was then told that one observer noted an apical diastolic murmur but that this observation was not confirmed by others. She remained generally in good health until 3 years before the present admission, when she developed shortness of breath, fatigue, and peripheral edema. In spite of digitalis, sodium restriction, and the frequent administration of mercurial diuretics, these disabilities persisted to such a degree that she was severely disabled for most of this period. At the time of her admission to the Peter Bent Brigham Hospital, she required abdominal paracentesis every fortnight.

On physical examination she had manifest edema and ascites. There was a medium-sized left pleural fusion and a small amount of fluid on the right. The heart was enlarged. A grade-I systolic murmur was heard at the apex and a faint diastolic muplop over the midprecordium. The liver edge was felt 5 cm. below the right costal margin. The vital capacity was 2500 ml.; arterial pressure was 10/80; venous pressure was 200 to 250 mm. of water; and the circulation time was (Decholin) 27 seconds. X-ray showed an enlarged heart without

TABLE 1.—Some Causes of Myocardial Fibrosis

1. Coronary artery disease
a. acquired
b. congenital
2. Constrictive pericarditis associated with myocardial fibrosis
3. Inflammatory
a. rheumatic fever
b. diphtheria
c. suppuration
d. trichinosis
e. virus infections
f. Chagas disease
g. toxoplasmosis
h. Fiedler's myocarditis
i. rickettsia
j. miscellaneous
4. Nutritional
a. endomyocardial fibrosis
5. Chemical
a. chloroform
b. phosphorus
c. carbon monoxide
d. benzol
e. miscellaneous
6. Systemic diseases
a. amyloid
b. glycogen storage
c. anemia
d. hemochromatosis
e. scleroderma
f. sarcoidosis
g. xanthomatosis
h. myotonia atrophica
i. Friedreich's ataxia
j. progressive muscular dystrophy
7. Obscure
a. congenital idiopathic hypertrophy
b. adult idiopathic hypertrophy
c. chronic fibroplastic myocarditis
d. idiopathic right cardiac hypertrophy
e. miscellaneous

evidence of calcification. On fluoroscopy, the amplitude of pulsation was diminished along all borders. An electrocardiogram showed right bundle-branch block. Cardiac catheterization showed moderately diminished cardiac output per minute and per beat; plateau of pressures from the "pulmonary capillaries" to the right atrium; low right ventricular pulse pressure, and pressure curves in the right atrium and right ventricle considered to be compatible with constrictive pericarditis. Thoracotomy was undertaken hopefully but direct vision showed a normal pericardium and a

myocardium that appeared to be irregularly mottled. The mottling seemed to be due both to subepicardial fat and to scarring in the myocardium. No obstruction was demonstrated in the inferior vena cava or in the left pulmonary vein. The conclusion was that the patient had myocardial fibrosis.

3. *R.C. PBBH 7F475*. This patient was a 37-year-old housewife who had good general health throughout most of her life. During a pregnancy 6 years before admission to this hospital, she was hospitalized because of pleuritic pain and, at this time, was found to have atrial fibrillation. Pain and arrhythmia disappeared after delivery; she regained her usual good health and continued to be well until about a year before admission. At this time she developed shortness of breath and fatigue. Both of these grew worse progressively and were eventually incapacitating.

When she entered the hospital she had an obviously enlarged heart, well marked venous distention, fluid in both pleural cavities, and a "questionable" diastolic murmur. X-ray examination showed cardiac enlargement and also demonstrated pulmonary vascular congestion and an enlarged pulmonary artery. No calcification in relation to the heart was seen. An electrocardiogram showed atrial fibrillation, small QRS complexes, and abnormal but nonspecific T-wave changes. The venous pressure was 200 mm. of water and remained elevated in spite of careful treatment and progressive loss of weight.

Cardiac catheterization showed low cardiac output, low stroke volume, and low right ventricular pulse pressure. She had the familiar plateau of pressure from peripheral veins to "pulmonary capillaries." The atrial pressure tracing showed the so-called "M" form and the right ventricular tracing showed a diastolic "dip." These findings, in the presence of intractable cardiac failure, suggested constrictive pericarditis as a hopeful possibility. An exploratory thoracotomy was carried out. When a normal pericardium was found, it was decided to examine the mitral orifice for a possible source of this patient's disability. The mitral valve was of normal size. Examination of a specimen of the left atrium taken at the same time showed focal thickening of the endocardium, but no clear evidence of rheumatic activity.

She continued to exhibit intractable and progressive congestive failure and in 1957 reentered the hospital. At this time, she was severely dyspneic and orthopneic. Physical examination revealed a pulse rate of 76 and a blood pressure of 100/60. There was no pulsus paradoxus. Cyanosis was noted and massive anasarca was present. The vital capacity was 700 ml. and the venous pressure

was 320 mm. of water. Despite intensive therapy, the patient remained in severe congestive heart failure and died. Postmortem examination revealed extensive focal myocardial fibrosis.

4. *G.S. PBBH*. This 39-year-old man was admitted to the hospital because of progressive dyspnea of 2 years' duration. He had been entirely well until 2 years before admission, when he developed exertional dyspnea, orthopnea, and a nonproductive cough. He was admitted to another hospital where he was found to be in congestive failure, although the cause of his failure was not apparent. He was treated with digitalis, diuretics, and a low-salt diet. Despite these measures he continued to have progressive symptoms.

Physical examination revealed a chronically ill white man. There were neck vein distention, generalized cardiomegaly, pulsus alternans, a diastolic gallop, and hepatomegaly. An electrocardiogram showed sinus tachycardia, numerous ventricular premature beats, and intraventricular block. Venous pressure was 204 mm. of water. A chest film showed an enlarged, globular heart with prominent hilar vessels suggesting pulmonary congestion. Right-sided cardiac catheterization revealed a low cardiac output. No pressure plateau was present; the "pulmonary capillary" pressure measured 39 mm. Hg while the right atrial pressure was 16 mm. Hg. A diagnosis of probable myocardial disease was made. Several weeks after discharge the patient died. Postmortem examination showed extensive fibrinoid degeneration of the left atrium and left ventricle. There was also widespread myocardial fibrosis in many areas of the left ventricle.

5. *N.L. PBBH 7E569*. This patient entered the hospital in 1954 at the age of 15. He exhibited severe congestive heart failure with extensive peripheral edema and persistent ascites. He had been disabled for a number of years. At the age of 7, he developed a streptococcal pharyngitis which was treated with sulfonamide. After this illness, he continued to suffer from persistent fatigue and a chest film was reported to show cardiac enlargement. In 1948, when studied at the Children's Medical Center, he showed obvious and persistent heart failure. In 1950, 4 years before his final admission, cardiac catheterization showed a low cardiac output per minute and per beat and a right ventricular diastolic "dip." Venous pressure at this time was 218 mm. of water. The patient did not have a plateau of pressures and the right ventricular pulse pressure was 26 mm. Several aspects of the general picture failed to support the diagnosis of constrictive pericarditis, but this diagnosis was not considered to be ruled out and an exploratory thoracotomy was per-

formed. A normal pericardium was found. The pericardium appeared to contain fat but no more specific evidence of myocardial disease could be obtained by inspection. After the operation, the patient followed a slowly progressive, deteriorating course. He developed atrial fibrillation. The size of the liver and spleen increased. Ascites recurred and edema was persistent. Venous pressure remained high throughout the course of his disease. Eventually, this patient developed multiple peripheral arterial emboli and died in circulatory shock. At postmortem examination diffuse myocardial fibrosis was found.

6. *F.O'C. PBBH 9D138*. This patient was a physician of 56 years whose history differed from the previous patients. He entered the hospital because of cardiac failure, which had begun only 6 months before admission, and which had followed a severe respiratory infection with fever and prostration. After some 6 weeks of this infection, he experienced severe fatigue and developed atrial fibrillation, edema, and ascites. These symptoms increased in severity in spite of skillful management with digitalis, diuretics, and sodium restriction. At the time of admission, he looked ill and tired. He was dyspneic and orthopneic. The heart was enlarged. A diastolic gallop rhythm was heard but there were no murmurs. Peripheral blood pressure was 106/70. There were fluid collections in both pleural cavities and the abdomen and marked pitting edema of the legs. Venous pressure was 320 mm. of water and circulation time (Decholin) was 38 seconds. X-rays of the heart confirmed the enlargement observed on physical examination. Fluoroscopic examination showed a beat of poor amplitude. No calcification was observed. An electrocardiogram showed small QRS complexes and nonspecific T-wave changes.

Cardiac catheterization showed a greatly reduced cardiac output per minute and per beat, but did not show a pressure plateau. A right ventricular diastolic dip was observed and there was a relatively high right ventricular pulse pressure (41 mm.). The observations made by way of the cardiac catheter were thus considered to be against the probability of constrictive pericarditis, although the onset of his illness in association with an infection, the rapid development of intractable failure, and the absence of hypertension and valvular disease were consistent with the possibility of constriction. A thoracotomy was carried out as the only decisive diagnostic measure. At this operation, a normal pericardium was seen. The appearance of the myocardial surface was considered by the surgeon to be consistent with a diagnosis of myocardial fibrosis. Postoperatively, the patient continued to do poorly and died approximately 2

years after operation. Postmortem examination was not made.

7. *W.Wa. PBBH*. This 58-year-old white plumber was admitted because of progressive heart failure of 8 years' duration. No accurate date could be established for the onset of his illness but it had started shortly after he received therapy for a staphylococcal infection of his left arm associated with blood stream invasion. Over the course of the next 8 years, he developed dyspnea, anasarca, and hepatomegaly. Physical examination showed a pulse rate of 62 and grossly irregular rhythm. Blood pressure was 115/75. There was marked neck vein distention. The heart was enlarged to the anterior axillary line. There were no significant murmurs. The venous pressure was 310 mm. of water and the circulation time was 61 seconds. Chest x-ray revealed a 13 per cent enlargement of the heart. An electrocardiogram showed atrial fibrillation and findings consistent with an old antero-septal myocardial infarct. Cardiac catheterization showed a stroke volume of 93 ml., a pulmonary capillary pressure that was 10 mm. Hg higher than his right atrial pressure, and a right ventricular pulse pressure that averaged 30 mm. Hg. All of these findings seemed somewhat against a diagnosis of constrictive pericarditis, but exploratory thoracotomy was performed. It showed a normal pericardium and a fibrotic myocardium. The patient was discharged home to be managed medically. No data are available as to his subsequent course.

8. *W.I. PBBH 8F182*. This patient was a 44-year-old farmer. He entered because of persistent and progressive heart failure of 10 years' duration. Physical examination showed a pulse rate of 72, and blood pressure of 100/64. The patient lay flat in bed without discomfort. The neck veins were distended. The heart was enlarged to the midaxillary line. The cardiac rhythm was grossly irregular. There were no significant murmurs. The signs of ascites were noted and the liver was palpable 5 cm. beneath the right costal margin. There was well-marked pitting edema of the ankles. The venous pressure was 280 mm. of water and the circulation time was 55 seconds. The chest x-ray showed generalized cardiac enlargement. The electrocardiogram showed atrial fibrillation and left bundle-branch block. At cardiac catheterization his pulmonary artery mean pressure exceeded his right atrial pressure by 11 mm. Hg. The marked cardiomegaly and the left bundle-branch block pointed to myocardial rather than to pericardial disease. In the faint hope that a surgically remediable lesion might be found, thoracotomy was performed but the pericardium was normal. The coronary arteries were calcified and in addition to fairly

diffuse fibrosis, there was a single scar (about 8 by 4 cm.) on the anterior surface of the right ventricle. The patient was discharged with a diagnosis of myocardial fibrosis secondary to coronary artery disease. No data are available as to his subsequent course.

9. *W.W. PBBH*. This 54-year-old white male engineer was admitted to the hospital because of a 4-year history of dyspnea, orthopnea, and peripheral edema. On physical examination he was an obese, chronically ill man. The arterial blood pressure was 135/85. There was a pulsus paradoxus of 15 mm. Hg. There were moist rales at both bases. The heart was moderately enlarged. There was normal sinus rhythm and a presystolic gallop, but no murmurs. There were hepatomegaly and severe pitting edema of the extremities. The venous pressure was 260 mm. of water, and the circulation time was 25 seconds. X-ray of the heart revealed a 15 per cent enlargement involving all chambers. There was no intracardiac calcification. The cardiac beat was diminished along all borders. The electrocardiogram was compatible with old posterior and anterior myocardial infarctions. Cardiac catheterization showed a low cardiac output. No plateau of pressures was present, the pulmonary capillary pressure exceeding the right atrial pressure by 10 mm. Hg.

Favoring a possible diagnosis of constrictive pericarditis were the relatively small heart and the presence of pulsus paradoxus. The electrocardiographic evidence of old myocardial infarctions and the lack of pericardial calcification favored myocardial disease. Although the weight of evidence favored myocardial fibrosis, this diagnosis was by no means certain. Therefore, an exploratory thoracotomy was performed. It revealed a normal pericardium. The myocardium was streaked with dense bands of fibrous tissue. The patient was discharged with a diagnosis of myocardial fibrosis.

The following 3 patients illustrate the clinical pattern of myocardial fibrosis. Cardiac catheterization was not performed in these patients but in each instance the diagnosis was confirmed by autopsy.

10. *P.M. NEDH*. This patient was a 13-year-old white boy who had been well until 6 months before admission, when swelling of the abdomen was noted. Shortly thereafter, he developed a sense of fatigue and was admitted to the New England Deaconess Hospital. On physical examination he appeared thin and chronically ill. The neck veins were distended. The left border of the heart extended to the anterior axillary line. The blood pressure was 100/80 mm. Hg, and a pulsus paradoxus was reported. There was ascites but no

peripheral edema. A presumptive diagnosis of constrictive pericarditis was made. Because of the worsening course of the patient, exploratory thoracotomy was undertaken promptly. During the induction of anesthesia the patient died. Post-mortem examination revealed a normal pericardium. There was considerable fibrosis of the myocardium involving both ventricles.

11. *H.W. PBBH 5J117*. This 60-year-old white housewife developed easy fatigability and dyspnea 6 years before the present admission. She was admitted to another hospital where she was found to be in congestive failure. She was treated with a low-salt diet, digitalization, and diuretics. Despite these measures, her congestive failure progressed. At this time, she was admitted to the Peter Bent Brigham Hospital.

Physical examination showed a chronically ill woman. There was visible venous distention, and moist inspiratory rales were present at both lung bases. The heart was enlarged to the anterior axillary line. There were frequent premature beats, both ventricular and atrial. There was a presystolic gallop at the apex. The liver was felt 4 cm. beneath the costal margin. There was minimal ankle edema. A venous pressure of 320 mm. of water and a circulation time of 45 seconds were recorded. Chest x-ray showed diffuse enlargement of the heart. An electrocardiogram indicated left bundle-branch block. Despite intensive therapy this patient continued to do poorly and approximately 1 year after her discharge from the hospital she died. Post-mortem examination showed evidence of an old myocarditis with replacement of large segments of the myocardium by fibrous tissue.

12. *L.A. (Not hospitalized)*. This 64-year-old white man had suffered myocardial infarction 4 years before he was seen by us and after this had developed intractable cardiac failure. When seen, he was bedridden and troubled by weakness, shortness of breath, and anasarca. Physical examination showed a chronically ill, cachectic man. The pulse rate was 102 and the blood pressure 105/90 mm. Hg. There was marked distention of the neck veins. There were bilateral basilar dullness and numerous moist inspiratory rales in this area. There was marked cardiomegaly with distant heart sounds. A protodiastolic gallop was present at the apex. The liver was palpable 4 cm. beneath the right costal margin. Severe pitting edema of the extremities and sacrum was present. In spite of intensive cardiac therapy, the patient continued to do poorly and ultimately died. Postmortem examination revealed severe coronary atherosclerosis with narrowed coronary lumina but no complete occlusion. There was diffuse replacement of myocardium by fibrous connective tissue.

The 2 final patients are known to have had both myocardial fibrosis and constrictive pericarditis; therefore, they offer special and instructive diagnostic problems.

13. *L.K. PBBH 5H602*. This 48-year-old white merchant entered the hospital because of progressive congestive heart failure of 8 years' duration. Sixteen years before admission, he developed the first of many episodes of supraventricular paroxysmal tachycardia. These episodes were at first controlled by means of carotid sinus pressure but ultimately required the use of digitalis. Eight years before admission he began to suffer attacks of nocturnal dyspnea. Five years before admission he developed fever and pleuritic pain. Diagnostic studies did not identify any specific etiology but he was treated with penicillin, digitalis, cortisone, and Dicumarol. Three weeks before his final admission, he was found to have marked cardiomegaly, numerous ventricular premature beats, pleural effusion, hepatosplenomegaly, and ankle edema. The venous pressure was 250 mm. of water, and the circulation time was 45 seconds. Despite mercurial diuretics, he continued to accumulate fluid and was admitted to the hospital. One of his chief discomforts was persistent pain in the right upper quadrant.

On physical examination the blood pressure was 100/70 mm. Hg and the pulse rate was 72 with numerous ventricular premature beats. The neck veins were distended. There was evidence of a right-sided pleural effusion. There was marked enlargement of the heart. There were a faint apical diastolic gallop and a grade-I whistling systolic murmur that radiated to the left axilla. The liver was felt 14 cm. below the right costal margin and the spleen was felt 8 cm. below the left costal margin. There was minimal ankle edema. X-ray revealed diffuse enlargement of the heart involving all chambers. The electrocardiogram was consistent with an old anteroapical myocardial infarct, and showed numerous ventricular premature beats of multifocal origin. The venous pressure was 255 mm. of water, and the circulation time was 40 seconds. Because of myocardial irritability, it was decided that cardiac catheterization should not be performed.

There was general agreement that a diagnosis of constrictive pericarditis was unlikely because of the extremely large heart. However, the possibility of this disease led to a decision to explore. At operation diffuse adhesions were found indicative of an old inflammatory process involving the anterior mediastinum. This process had produced both constrictive pericarditis and constrictive pleuritis. The pericardium was stripped with difficulty

as the fibrotic process extended into the epicardial layer of the myocardium.

Following pericardiectomy, the patient did relatively well for approximately 12 days and for the first time in years was free of discomfort in the liver region. Then he was found dead in bed and the presumption was that he died of a ventricular arrhythmia. Postmortem examination was not performed, but the appearance of his myocardium at surgery made it clear that he had diffuse myocardial fibrosis.

14. *E.F. PBBH 6B132*. This 44-year-old school teacher was observed at the Peter Bent Brigham Hospital for a period of 17 years. In 1937, he developed an acute tuberculous pericarditis. Five months after the acute phase of this illness, he showed the manifestations of constrictive pericarditis. The anterior half of his pericardium was resected but he continued in congestive heart failure. During the long period of observation, 3 more attempts to alleviate his failure by means of pericardial resection was made and all failed. He continued to show peripheral venous hypertension, a low cardiac output, pulmonary congestion, anasarca, and hepatosplenomegaly. He ultimately died of congestive failure, and postmortem examination revealed diffuse myocardial fibrosis. This myocardial fibrosis had resulted from the same process that had given rise to constrictive pericarditis and explained the progressive downhill course, which continued after relief of the pericardial constriction. In our experience, myocardial fibrosis and constrictive pericarditis are frequently seen in combination. The myocardial fibrosis is frequently a factor limiting the degree of relief obtained by surgery for constrictive pericarditis.³

DISCUSSION

Approximately 25 years ago chronic myocarditis or myocardosis was a popular and frequent diagnosis. It was defined as a lesion in which cardiac failure was associated with normal valves and pericardium while the heart muscle showed hypertrophy, alone or in combination with fibrous interstitial myocarditis.⁴ According to Cabot,⁵ it was the most frequent cause of failure seen in adult clinics. Subsequent work established that most of these patients had either hypertensive disease or coronary artery disease as a cause of their cardiac failure. The diagnosis of chronic myocardosis then received less and less attention until recent years, when the importance of diseases that specifically involve the myocar-

dium has again been emphasized.⁶ It has become obvious that the end result of many diseases affecting the myocardium may be diffuse myocardial fibrosis, and the patients presented in this paper may be considered as examples of the consequences of diffuse myocardial disease.

The anatomic situation was demonstrated in each patient by operation, postmortem examination, or both. In general, these patients with diffuse myocardial disease and without pericardial disease presented themselves with the manifestations of intractable heart failure. There was usually a definite onset in time. No patient in this group had clear evidence of valve disease; none had hypertension. The following phenomena were usually observed:

1. Elevated venous pressure
2. Congestive hepatomegaly (with or without congestive splenomegaly)
3. Ascites
4. Peripheral edema
5. Enlargement of the heart
6. Distant heart sounds
7. A diastolic gallop rhythm
8. Diminished cardiac pulsations under the fluoroscope
9. Signs of peripheral congestion which were more impressive than those of pulmonary congestion
10. Electrocardiograms which showed low voltage and nonspecific T-wave changes
11. A disappointing response to treatment for congestive heart failure

These items are, in general, similar to those observed in patients with constrictive pericarditis. The elevated venous pressure of myocardial fibrosis is indistinguishable from that of constrictive pericarditis, and in both disorders the venous pressure remains high in spite of treatment. Phlebotomy or diuresis may lower it temporarily but it soon returns to its previous level.

Emphasis has been given by many authors to the absence of extreme cardiac enlargement in patients with constrictive pericarditis and this has sometimes been interpreted to mean that the heart in such patients is not enlarged. Actually, most patients with this disease do

have cardiac enlargement. On the whole, however, the heart size is less than experience leads one to expect in a patient with the degree of congestion presented by these individuals. Therefore, a high degree of cardiac enlargement tends to tilt the scales in favor of myocardial fibrosis. It does not, however, prove the point, and one patient (no. 10), who had a very large heart and who was thought for this reason to have myocardial fibrosis, turned out at operation to have both constrictive pericarditis and myocardial fibrosis.

The electrocardiogram in these 2 conditions is likely to show a general similarity. If there is a characteristic pattern of infarction, this also tends to tip the scale toward myocardial rather than pericardial disease, but again, does not prove the point. The similarity in the electrocardiograms of patients with pericarditis and those with coronary disease is so marked as to constitute in our experience a demonstration that the electrocardiogram associated with coronary disease is not truly specific but simply points to an abnormality of the myocardium. No doubt coronary disease is the commonest cause of such abnormality but the tracing is nonspecific. Dr. Harold Levine,⁷ in analyzing 35 patients with proved constrictive pericarditis, reported that 4 showed preoperative electrocardiograms diagnostic of old myocardial infarction. Eight more had curves compatible with old myocardial infarction. He concluded that the diagnosis of constrictive pericarditis should not be surrendered simply because the electrocardiogram points to an old myocardial infarction.

One of the most characteristic findings in both these groups of patients is an intractable course resistant to treatment. In our experience, nothing about the course or the reaction to treatment can serve to differentiate one from another.

The history of an original injury to either pericardium or myocardium may be significant. If there is a good history of acute pericarditis or a good history of myocardial infarction, one can start out with an etiology for constrictive pericarditis on the one hand

of myocardial fibrosis on the other. The weight one gives to this evidence depends on the thoroughness of the documentation.

Pulsus paradoxus may occur in both conditions but in our experience has been more frequent and more impressive in patients with constrictive pericarditis than in those with myocardial fibrosis.

Characteristic calcification involving the pericardium is present in about half of our patients with constrictive pericarditis. Its presence is, therefore, evidence in favor of this diagnosis. Since 50 per cent of our patients with constrictive pericarditis do not show calcification at all, its absence is not conclusive. Ten of our 14 patients underwent cardiac catheterization.¹ One may say that the general pattern of intravascular pressures in these patients has certain similarities to the pattern observed in constrictive pericarditis. Each patient had a diminished cardiac output and a low stroke volume. The right ventricular pulse pressure varied from 8 to 45 mm.; in general this measurement tended to be below the normal level but was usually not reduced to the degree observed in constrictive pericarditis. The pressures in the pulmonary artery and the systolic pressure in the right ventricle tended to be higher in myocardial fibrosis than in constrictive pericarditis, but the levels overlapped. Most patients in whom satisfactory pressure tracings were obtained exhibited the so-called right ventricular "diastolic dip" and the right atrial "M."

In contrast to most patients with constrictive pericarditis, some of these patients did not have a plateau of pressures, i.e., the pulmonary capillary pressure exceeded the right atrial pressure by more than 5 mm. Hg. Patients with this finding who were examined post mortem were shown to have predominantly left ventricular fibrosis. Patients with fibrosis of both ventricles did show a plateau of pressures and the catheter findings were indistinguishable from those of patients with constrictive pericarditis.

The ingenious work of Isaacs and his co-workers⁸ on unilateral pericardial constriction showed that the absence of a pressure plateau

does not necessarily rule out constrictive pericarditis. In our experience, however, the absence of a pressure plateau weights the scales on the side of myocardial constriction.

It is apparent that neither physical findings, course, nor catheterization measurements permit a specific differentiation between myocardial fibrosis and pericardial constriction. The similarities of the clinical and hemodynamic patterns of myocardial fibrosis and constrictive pericarditis have also been noted by Nye, Lovejoy, and Yu.⁹ The similarity of the manifestations of these 2 disorders indicates that the effect of fibrosis on the distensibility characteristics of the heart are similar whether the fibrosis is localized to the myocardium or the pericardium. Indeed, it is now known from the work of Clark, Ballentine and Blount¹⁰ that similar manifestations may occur in a patient with endocardial fibrosis. Since these disorders affect cardiac hemodynamics in an identical fashion, it is to be expected that their signs and symptoms should be virtually identical. In many patients this difficult differential diagnosis can only be resolved by direct inspection of the heart.

SUMMARY

Diffuse myocardial fibrosis is a disease of diverse etiology; the commonest cause is coronary artery disease. Physiologically, it produces a restriction of diastolic filling and thus resembles constrictive pericarditis and endocardial fibroelastosis. Clinically, it resembles constrictive pericarditis so closely that in many patients the differential diagnosis between these 2 disorders can be resolved only by thoracotomy and direct observation of the pericardium.

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SUMMARIO IN INTERLINGUA

Diffuse fibrosis myocardial es un morbo de diverse etiologias. Le causa le plus commun es morbo de arteria coronari. Physiologicamente illo produce un restriction del replenation diastolic e assi resimila pericarditis constrictive e fibroelastosis endocardial. Clinicamente illo resimila pericarditis constrictive si intimemente que le diagnose differential inter le 2 conditiones pote esser effectuate in multe casos solmente per thoracotomia e le observation directe del pericardio.

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BEFORE LAENNEC

Give me a calm and thankful heart
From every murmur free . . .

From a hymn by Anne Steele, 1760

FROM C. SIDNEY BURWELL, M.D., AND JAMES METCALFE, M.D. *Heart Disease and Pregnancy. Physiology and Management*. Boston, Little, Brown and Company, 1958, p. 50.

ABSTRACTS

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ATHEROSCLEROSIS

Kuwabara, T., and Cogan, D.: **Experimental Aberrant Lipogenesis.** *Arch. Path.* 67: 34 (Jan.), 1959.

As with previously described experiments using oleate, sodium palmitate and sodium stearate were injected into the corneas of living rabbits and into excised corneal buttons, which were then incubated, or added to the serum in which corneal buttons or liver buttons were incubated. After a suitable incubation period sections were made and studied with appropriate stains, which indicated that palmitate and stearate resulted in the formation of a crystalline substance in the tissue cells analogous to the formation of sudanophilic globules in cells exposed to oleates. Autoradiographs with radioactive palmitate showed that palmitate anion was incorporated in the cells. When sodium stearate or palmitate were added to a medium containing oleates the cells developed both a sudanophilic and crystalline lipid, suggesting that the effects were additive and apparently independent with no evidence of inhibition of activity. Similar findings were noted in the liver experiments. While identification of the end products was not made, it appeared that they had the histochemical properties of neutral fats and phospholipids.

MAXWELL

Seskind, C. R., Schroeder, M. T., Rasmussen, R. A., and Wissler, R. W.: **Serum Lipid Levels in Rats Fed Vegetable Oils with and without Cholesterol.** *Proc. Soc. Exper. Biol. & Med.* 100: 631 (Mar.), 1959.

The degree of saturation and the fatty acid distribution of dietary fat are reputedly important in affecting serum lipid levels. The reported study was designed to determine the effects of a known atherogenic diet on serum lipid levels in rats with source of fat and presence or absence of cholesterol as the only variables. In general, the serum level of cholesterol was correspondingly elevated by increasing saturation of the dietary fat and, furthermore, dietary cholesterol augments this effect. Elevation was transient for the less saturated oils but was more sustained for highly saturated oils. In general, serum phospholipid values paralleled those of cholesterol. Only by feeding fats with the lowest iodine number was there an elevation of phospholipid levels to especially high values as compared with serum cholesterol. The cholesterol phospholipid ratio showed no difference between groups fed high iodine number oils with or without dietary cholesterol. The more saturated fats showed elevation of ratios in groups with added cholesterol above groups fed no cholesterol. Highly saturated fats fed alone had a lowering effect on the cholesterol phospholipid ratio.

KRAUSE

Engelberg, H.: **Effect of Epinephrine Upon Plasma Optical Density, Unesterified Fatty Acids, Lipemia Clearing and Heparin Levels.** *Proc. Soc. Exper. Biol. & Med.* 100: 492 (Mar.), 1959.

Epinephrine is important in the physiology of fat mobilization and the plasma unesterified fatty acid is the major fat transport mechanism in-

volved in this effect. Furthermore, it has been demonstrated that increased triglyceride lipolysis in fat depots follows epinephrine injection and that unesterified fatty acids are released. No data have been obtained on plasma lipemia clearing activity or on heparin levels. Since the heparin lipoprotein lipase system probably plays a role in removal of alimentary lipemia and perhaps in tissue triglyceride lipolysis, these studies were designed to supply data on the effect of epinephrine upon plasma optical density, unesterified fatty acids, lipemia clearing, and heparin levels. The data were obtained by using 0.1-0.2 ml. of 1:1000 epinephrine intravenously in 9 dogs, and 1 ml. of 1:1000 epinephrine solution diluted with 100 ml. of saline as a continuous intravenous infusion for 20 minutes in 4 individuals. There was no change in the plasma optical density nor lipemia clearing activity. Unesterified fatty acids were definitely increased in both the dogs and human subjects. Circulating heparin was increased in 3 of the 4 individuals studied. It was concluded that elevation of unesterified fatty acids did not occur as a result of enhanced plasma triglyceride lipolysis, and that the rise in heparin was probably part of a stress reaction unrelated, in this instance, to its role in fat transport.

KRAUSE

Prior, J. T., Rohner, R. F., Camp, F. A., and Rustad, H.: *The Effects of Cortisone upon Aortic Intimal Repair in the Hypercholesteremic Rabbit*. *Arch. Path.* 67: 159 (Feb.), 1959.

Alterations in the pattern of aortic injury and repair produced by the administration of cortisone plus dietary cholesterol were studied in white rabbits. Six animals maintained on 15 mg. of cortisone acetate daily showed diffuse fatty liver, muscle necrosis and calcification, pulmonary infections, kidney abscesses, and swelling and degeneration of the cells in the zona fasciculata, but no changes in arteries. Another group received the same dosage of cortisone plus 1 Gm. of oral cholesterol daily and again showed neither gross nor microscopic atherosclerotic changes, although in a previous study the authors had shown that on an identical diet, but without cortisone, animals developed microscopic and gross aortic intimal lesions well before the end of the 2 month experimental period. Another group was subjected to aortic injury by needling the aorta and were in addition given cortisone. In this group very little regenerative activity and no marginal inflammatory reaction were observed in the first 10 days following trauma. In this group there was noted delayed and atypical in-

flammatory and reparative reaction within the injured aortic segment. The largest group of animals consisted of hypercholesteremic and cortisone-injected rabbits with traumatized aortas. Lesions in this group were also characterized by atypical changes and a striking lack of lipophages such as was found in cortisone-injected animals with trauma. This absence of lipophages is true only at the high cortisone levels which in the control group produced the various visceral lesions. When cortisone dosage was less, the animals tended to show the changes characteristic of trauma with cholesterol alone, which are not described in this article, reference being made to previous publications by the authors. It is suggested by the authors that the lack of histocytic elements in the cortisone-injected animals might explain the observed retardation of atherogenesis.

MAXWELL

BLOOD COAGULATION AND THROMBOEMBOLISM

Desrochers, Y., Aerichide, N., and David, P.: *Anticoagulant Therapy: Clinical Experience with Acenocoumarin (Sintrom) and Other Coumarin Derivatives*. *Am. Heart J.* 57: 321 (Mar.), 1959.

The treatment of 382 patients with anticoagulant drugs is described with particular attention directed to 305 who received acenocoumarin (Sintrom). Acenocoumarin was found to be a more satisfactory agent than either bishydroxycoumarin or ethyl biscoumacetate in clinical use. Its duration of effect was substantially shorter than that of bishydroxycoumarin but still was sufficiently long for satisfactory maintenance of effect on a single daily dose. Therapeutic hypoprothrombinemia could be obtained in 2 to 3 days with acenocoumarin and usually could easily be reversed by discontinuing the drug without adding vitamin K. The dose of acenocoumarin employed in this study was considerably lower than that recommended elsewhere. The optimum loading dose was 11 to 25 mg. over a period of 18 to 60 hours, and an average of 3.6 mg. daily was found to be a satisfactory maintenance dose. Hemorrhagic and thromboembolic accidents were infrequent in this series. The Quick method for determining prothrombin time was an adequate measure of the efficacy of anticoagulant therapy. In the 287 patients with coronary artery disease the mortality appeared to be markedly reduced by anticoagulant therapy.

SAGALL

Shlachman, M., and Cavusoglu, M.: **Practical Application of Heparin for Long-Term Anticoagulant Therapy.** New York State J. Med. 59: 1054 (Mar. 15), 1959.

In the opinion of many authorities heparin is a more desirable anticoagulant than the oral coumarin derivatives. However, because of the disadvantage of repeated intravenous injections, heparin has not had widespread use. Attempts to use heparin in a depository form have demonstrated this method to be painful and erratic in action. When used intramuscularly in a concentrated aqueous solution, heparin causes much pain and occasionally hematomas. In this study, 14 patients received subcutaneous injections of 1 ml. of a concentrated aqueous solution of heparin (200 mg. per ml.). Therapeutic anticoagulation was obtained within 2 hours in all but 5 patients and within 4 hours in all but 1 patient. At the end of 8 hours, the anticoagulation effect began to taper off but was still at a therapeutic range in 27 patients. Only 7 patients showed satisfactory anticoagulant effect at the end of 12 hours. Eighteen patients were given 150 mg. of heparin subcutaneously every 12 hours for a 3-day period. This regimen produced a constant therapeutic anticoagulant effect. One patient developed slight hemoptysis and another exhibited ecchymoses at the injection site. This comparative lack of untoward reactions made it unnecessary to perform repeated tests of the coagulation time. Since this method of heparin administration was simple, painless, and safe, it seemed a practical way to carry out anticoagulant therapy. The procedure may be carried out by lay people or may even be self-administered under the supervision of a physician.

KRAUSE

CONGENITAL ANOMALIES

Kreel I., Reiss, R., Strauss, L., Blumenthal, S., and Baronofsky, I. D.: **Supra-Valvular Stenosis of the Aorta.** Ann. Surg. 149: 519 (April), 1959.

Five cases of a stenosing lesion of the aorta situated above the aortic valve have been found in the literature and this report deals with 1 additional case described in detail. The clinical picture has been one of congestive failure, chest pain, and systolic and diastolic murmurs. The average age of survival is reported as 39 years. Rheumatic endocarditis was found in 1 case. In 3 others there have been associated anomalies such as Marfan's syndrome, bicuspid aortic valve, and congenital aortic aneurysm. In the patient reported here a systolic murmur was noted from the age of 3 months, left ventricular enlargement from the age of 3 years, and an

aortic diastolic murmur at 10 years. For 5 months prior to admission, there had been definite anginal distress. A systolic murmur was heard at the right second intercostal space with radiation to the neck and back. An early diastolic murmur was noted at the left sternal border in the third and fourth intercostal spaces. An attempt was made at surgical repair employing cardiac bypass. The lesion consisted of a thick circular ridge that narrowed the aorta just above the sinus of Valsalva. All 3 cusps were thickened and the right coronary cusp was adherent to the aorta covering the orifice of the right coronary artery. These thickened tissues consisted largely of increase in collagenous fibers and cellular connective tissue rich in basophilic ground-substance. The obstructing ring seemed to be continuous with the aortic media. Dilatation of the ring was followed by intractable dilatation of the left ventricle and it was believed that an increased degree of aortic insufficiency had been produced as a result of the fixation of the right aortic cusp to the aortic wall in the open position. Because of the gravity of the prognosis in these cases it is felt that surgery should be attempted. Therapy of choice at this time is manual dilatation or actual excision of the obstructing ring if possible. It may be that angiocardiology and left heart catheterization will permit a more accurate diagnosis preoperatively in those cases of aortic valve disease that present unusual variations of history and physical findings from the average case.

LEVINSON

CONGESTIVE HEART FAILURE

Gavosto, F., Buffa, F., and Chiarle, S.: **Behavior of Serum Alphaketo-Glutaric Acid in Congestive Heart Failure.** Acta cardiol. 13: 618, 1958.

The mean value of serum α -ketoglutaric acid in normal subjects was found to be 0.211 ± 0.093 mg. per cent. An increase in this value was found in some patients with congestive heart failure and the rise in α -ketoglutaric acid levels was shown statistically to be related to the degree of failure. Serum pyruvic levels, studied in the same patients, were not found to relate to the degree of failure.

BRACHFELD

CORONARY ARTERY DISEASE

Kenamer, R., and Prinzmetal, M.: **Treatment of Angina Pectoris with Catron (JB 516).** Am. J. Cardiol. 3: 542 (April), 1959.

Catron, a monamine oxidase inhibitor related to amphetamine, was administered for as long as 9 months to 31 patients having severe angina

pectoris. The most satisfactory dose was 6.25 mg. given twice daily. Moderate or marked improvement was noted in 23 patients, usually beginning several days after onset of therapy. Electrocardiographic improvement was not seen, and the mechanism of Catron's action is unknown. Side effects were observed in 13 patients, including principally postural hypotension in 5 and insomnia or jitteriness in 6. These effects usually became tolerable when the dosage was lowered. Catron was deemed to be worthy of extensive trial in angina pectoris.

ROGERS

Ahronheim, J. H., and Wagman, G. F.: Dissecting Hemorrhage in Media of Coronary Artery. *Arch. Path.* 67: 19 (Jan.), 1959.

This paper consists of the presentation of a case of a 41-year-old woman who died suddenly and in whom a dissecting hemorrhage in the mediae of the ramis interventricularis posterior of the right coronary artery was found. Associated with this hemorrhage were periadventitial inflammatory infiltrates suggestive of polyarteritis, but similar infiltrates were not found in any other arteries examined at autopsy.

MAXWELL

Wilgram, C. F.: Experimental Atherosclerosis and Cardiac Infarcts in Rats. *J. Exper. Med.* 109: 293 (Mar.), 1959.

The rat demonstrates spontaneous coronary lesions with age, consisting usually of lipomatous intimal lesions or diffuse fibrosis and hyperplasia. In these experiments a Moenekeberg type of medial sclerosis as well as calcification, splitting of the internal elastic membrane and pronounced degrees of proliferation and lipid accumulation in the subintimal layer were noted. Frequently thrombosis and occlusion of the arterial lumen were seen in the latter. Cardiac infarction was distinguished from cardiac focal necrosis by a wall of leukocytes surrounding the necrotic tissue. The rats used in these experiments were either younger than 2 years at the time of sacrifice or died before reaching this age, so that spontaneous changes were rarely seen. Cholesterol feeding alone induced only lipomatous changes, probably due to the ability of the rat to metabolize exogenous cholesterol efficiently. Exposure to cold only increased lipomatous changes. The incidence of coronary lesions was not affected by adrenalectomy. The addition of viosterol to the cholesterol diet produced a Moenekeberg type of medial sclerosis with death usually due to nephrocalcinosis. When thiouracil was added to the above regime, 64 per cent had severe athero-

sclerosis. The omission of viosterol reduced the severity of these lesions. One third of the rats in the cholesterol-fed, viosterol and thiouracil added, regime had coronary occlusion caused by severe atherosclerosis; one-half of these had myocardial infarcts. It appeared that vascular injury, as induced by viosterol, was necessary to produce significant atherosclerosis in the rat. Peculiarities of the coronary circulation or differences in the clotting mechanism were given as the explanation for the relatively low incidence of myocardial infarction in those rats having a coronary occlusion. The term "vascular injury" is an intangible quantity. It is not intended that these findings be applied directly to human pathology. The data do not support the vascularization theory of atherosclerosis, since there are no vaso vasorum in the rat.

LEVINSON

Vasicka, Al. I., and Lin, T. J. Fatal Coronary Artery Disease During the Early Postpartum Period. *Am. J. Obst. & Gynec.* 77: 899 (April), 1959.

A 21-year-old woman died suddenly on the fourth postpartum day following the delivery of a stillborn baby at the fortieth week of gestation. The postpartum course was characterized by hypokaliemia, which was recognized on the third day postpartum. (The serum potassium taken immediately after death was 2.1 meq. per ml.) An electrocardiogram taken on the third day showed frequent ventricular ectopic beats, transient first-stage atrioventricular block and a Q-T (or Q-U) interval of 0.62 second. The S-T segment was markedly depressed and upwardly concave in all the standard and unipolar limb leads except aV_F, and in the precordial leads from V₂ to V₆. The T wave was terminally upright in all leads in which the S-T segment was depressed. The record was considered to be consistent with hypokaliemia. At autopsy there was a recent subendocardial infarct in the left ventricle and interventricular septum. There was coronary arteriosclerosis with marked stenosis of the anterior descending branch of the left coronary artery. There was moderate arteriosclerosis of the aorta. The values of serum cholesterol had not been obtained in this patient. There was no family history of significance. There was no previous evidence of long-standing hypokaliemia in the patient or the family. However, no blood relative had been found. It is suggested that the hypokaliemia aggravated the coronary artery disease and contributed to the fatal outcome in this patient.

SHEPS

ELECTROCARDIOGRAPHY, VECTOR-CARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNIQS

Vinsor T., and Karpman, H.: **The Morphology of Normal and Abnormal Pulse Waves Recorded Plethysmographically.** *Am. J. Cardiol.* 3: 511 (April), 1959.

The results of plethysmographic studies in over 100 patients having various cardiovascular lesions were compared with those in normal subjects. A direct-writing electronic plethysmograph was used on the digits, and a different instrument was used for segmental limb studies. The important pulse wave characteristics from several areas were depicted and described including crest time, rate of rise of anacrotic limb, wave amplitude, and pulsation ratio between arm and leg, half rise time, presence of a dicrotic notch, rate of volume change, and inclination time. Distal to an obstruction (e.g., from arteriosclerosis) the waves were low and rounded, had delayed rise, crest, and inclination times, tended to lose the dicrotic notch, and showed harmonic vector abnormalities. High cardiac output states showed waves increased in amplitude with more rapid rise and fall times and an accelerated pulse velocity. Proper evaluation of the tracings was found useful both in diagnosis and in following the effects of treatment of a variety of circulatory disorders.

ROGERS

de Oliveira, J. M., and Zimmerman, H. A.: **Angular Overloadings. Electrocardiographic Analysis of 193 Cases.** *Am. J. Cardiol.* 3: 453 (April), 1959.

P waves were examined in 41 patients with mitral valve disease, in 100 with congenital heart disease, and in 52 with diffuse pulmonary lesions. Clinical, hemodynamic, and, in 20, vectorecardiographic correlations were made. Left atrial overloading was characterized by notching and increased duration of P waves in the limb and left precordial leads and by a marked backward orientation of the P vector. Left atrial dilatation usually was associated with increased P-wave duration, but hypertrophy without dilatation was occasionally present when P-wave duration was normal. Right atrial overloading was characterized by peaking and heightening of P waves in the limb and right precordial leads and by a deviation of the P axis to the right (of ± 60 degrees) without appreciable increase in P-wave duration. These changes were attributed to 1 or more of 3 factors: hypoxia, increased flow or pressure in the right atrium, a change in the

position of the heart. When the right atrial systolic pressure was 10 mm. Hg or higher the P waves were regularly 2 mm. or taller. However, taller P waves might be seen with lower pressure when 1 or both of the other 2 factors were present. For this reason, it was not possible to determine by the "auriculogram" whether cor pulmonale was present in patients with chronic hypoxia. Biatrial overloading could be suspected when combinations of the signs described above were present.

ROGERS

Graybiel, A., and Allebach, N. W.: **The Work Electrocardiogram.** *Am. J. Cardiol.* 3: 430 (April), 1959.

Experience with 400 patients having electrocardiograms before and after various types of effort is described, and 14 illustrated case histories are presented. While the exertion was preferably performed on a treadmill, the use of a 20-inch step test was found to be satisfactory. Increments of work were carried out until electrocardiographic abnormalities appeared or until the patient demonstrated an adequate effort tolerance. In selected instances, the electrocardiographic response to breathing 100 per cent oxygen (attempting to reverse ischemic changes), to Levy's anoxia test, to ingesting 100 Gm. of glucose or 1.5 Gm. of potassium chloride, or to hyperventilation was tested as a supplementary study. Each electrocardiographic change after work was examined in order to assess its significance. The results of these evaluations may provide objective evidence of coronary insufficiency, especially when the symptoms are atypical.

ROGERS

Prinzmetal, M., Ekmecki, A., Toyoshima, H., and Kwocynski, J. K.: **Angina Pectoris: III. Demonstration of a Chemical Origin of ST Deviation in Classic Angina Pectoris, Its Variant Forms, Early Myocardial Infarction, and Some Noncardiac Conditions.** *Am. J. Cardiol.* 3: 276 (Mar.), 1959.

In angina pectoris, electrocardiographic leads overlying the ischemic myocardium usually show S-T segment depression, but occasionally S-T elevation is found (variant form). These phenomena were investigated clinically and also in a series of dog experiments in which the S-T elevation was produced by ligation of the coronary artery and S-T depression was induced by hypotension. The S-T deviations were only apparent and actually represented T-P segment deviations. S-T elevation, but not depression, was promptly abolished by washing the surface

of the ischemic heart with physiologic saline. Analysis of the ischemic myocardium producing S-T depression showed a decrease in intracellular sodium and an increase in intracellular potassium. An increased cardiac potassium uptake during S-T depression was confirmed by calculating the extraction of the ion from the perfusing blood. That intracellular potassium migration was closely related to S-T depression was demonstrated by the latter's appearance soon after 5 per cent glucose solution was injected into a ligated coronary artery. Injection into a coronary artery of hypertonic sodium or of hypotonic potassium solutions produced S-T depressions, and vice versa, apparently by altering the gradient of each ion across the cell membrane. The classical concepts of cardiac injury currents were examined in the light of the present findings. The S-T depression was thought to be due to the influences of ischemia on the subepicardial muscle. Prominent among these influences were the increase in intracellular potassium content and the increase in potassium ion gradient with resultant increase in resting membrane potential. That the S-T depression was not reciprocal to subendocardial ischemia was maintained from theoretical considerations and from electrocardiograms made via intracavitary leads. Whether S-T elevation represented merely a more severe degree of ischemia was being studied further.

ROGERS

Bauer, C. H., Engle, M. A., and Mellins, R.: Hypervagism and Cardiac Arrest. *Bull. New York Acad. Med.* 35: 260 (April), 1959.

Case reports are presented of 2 infants who exhibited signs of sinoatrial block due to vagal stimulation. The first patient had a large cystic goiter (due to congenital myxedema) that stimulated the carotid sinus; vagal stimulation in the second infant was caused by a dilated thoracic stomach (consequent to an esophagostomy for repair of an esophageal atresia). The authors recommended the use of atropine for therapy and prophylaxis of arrhythmias produced by vagal stimulation but, in addition, they noted that the bradycardia produced by vagal stimulation might also be treated with epinephrine or other sympathomimetic drugs such as Isuprel.

KARPMAN

Gomes Marques, M.: Partial Fibrillation of the Atria. *Cardiologia* 34: 233, 1959.

A case is described of a 72-year-old man with uremic pericarditis in which the electrocardiogram showed nodal rhythm with retrograde P waves and occasional extrasystoles with a P-R

interval of 0.10 second throughout the electrocardiogram. An independent set of deflections apparently atrial in origin, of low voltage (0. mV) was seen. These deflections were unrelated to the nodal rhythm and they occurred irregularly at intervals varying between 1.2 and 2.4 seconds. These waves were seen in limb leads except in lead I, and were particularly evident in leads II and III, where they were upright and occasionally diphasic. These deflections were indiscernible in chest leads. Each P wave was followed by a burst of rapid oscillations (rate about 2,500 per minute) lasting for 0.20 second up to 1 second and even more. These oscillations varied in amplitude, contour, and spacing, suggesting that they were caused by a fibrillatory activity. These reports were made photographically, on different occasions and in different rooms, with a cathode-ray oscillograph and a mirror galvanometer. Records were taken simultaneously, in the same rooms and with the same machines from other patients, this way discarding artifacts as an explanation to the superadded activity. The nature of the phenomenon is discussed. The author believes that it represents circumscribed atrial fibrillation similar to the case reported by Deitz and co-workers.

BRACHFELD

Doneff, D., and Scheid, H.: On the Wolff-Parkinson-White Syndrome. *Cardiologia* 34: 199, 1959.

Five patients with Wolff-Parkinson-White syndrome (4 in young athletes, one in a 42-year-old nurse) are described in detail. The Wolff-Parkinson-White syndrome was persistent in 1 patient and transient in the remaining ones. In all patients, clinical examination, supplemented by ergo-spirometry in 2 instances, gave normal results with respect to the cardiovascular system. A significant incidence of signs of autonomic nervous disorders was found. The medical assessment from the point of view of athletes is discussed. In accordance with the opinion of others, the presence of a Wolff-Parkinson-White syndrome in otherwise healthy young subjects is not regarded as indicating cardiac disease.

BRACHFELD

Edwards, E. A., Cohen, N. R., and Kaplan, M. M.: Effect of Exercise on the Peripheral Pulses. *New England J. Med.* 260: 738 (April 9), 1959.

The peripheral pulses in the legs of 11 normal subjects and 11 patients with arteriosclerosis recorded by an infratrac pulse oscillograph before and after exercise showed increased amplitude and systolic slope of the pulse at high (thigh or calf) levels and diminution at low (foot or toe) levels. These results indicated that with exercise

the blood was diverted to the working muscle and the blood flow to the distal parts was decreased. After sympathectomy the proportions of the pre-exercise and postexercise readings were unchanged, despite favorable results. This finding indicated that vasospasm played no part in the exercise response. The phenomenon of diminution of the pedal pulses in patients exhibiting claudication but with palpable pulses was confirmed. In these patients claudication did not result from arterial spasm, but was due to partial occlusion at aortic or iliac levels with resultant inadequate flow for the demands of exercise. The shift of blood away from the foot and toes during exercise explains why some patients develop pain in these parts on walking and indicates caution in the use of exercise for the ischemic foot.

SAGALL

HYPERTENSION

Pickles, B. G.: **Phaeochromocytoma Complicating Pregnancy.** *J. Obst. & Gynaecol.* 65: 1010 (Dec.), 1958.

The author presents a case report of a 26-year-old woman who died with acute pulmonary edema and a temperature of 107 F. 1 hour and 20 minutes after the delivery of her third child. All pregnancies had been normal with no toxemias and no recorded hypertension. At postmortem examination a pheochromocytoma was found in the right adrenal gland. Her only symptoms had been recurrent epigastric pain and palpitations. Previous reports of pheochromocytoma in pregnancy are reviewed and diagnosis is discussed.

MAXWELL

Paladini, A. C., Braun-Menendez, E., del Frade, I. S., and Massani, Z. M.: **The Estimation of Angiotensin in Blood.** *J. Lab. & Clin. Med.* 53: 264 (Feb.), 1959.

A method for the estimation of angiotensin in blood of dogs is described by utilization of only 50 ml. of arterial blood, thereby eliminating the criticism, previously made of other methods for angiotensin estimation, that the large volumes of blood required produced hypotension, which in turn elicited a renin response with formation of more angiotensin. Blood samples were collected into ethanol and angiotensin was removed from the filtrates by the resin Dowex 50-X. On elution with alkali, a solution was obtained that could be further concentrated and assayed for its pressor action by intravenous injection into small nephrectomized rats. The method was tested by adding 10 rat units of angiotensin to 50 ml. of heparinized dog blood just prior to extraction with ethanol, while another 50 ml. of the same

blood was processed simultaneously using the pressor value thus obtained as a blank for the first sample. The data presented indicated complete recovery of the added angiotensin. Addition of epinephrine or norepinephrine to blood produced no additional pressor activity, indicating that the catecholamines were destroyed during the processing. Added pepsitensin was completely recoverable, whereas added tyramine and vasopressin were recoverable only to the extent of 15 per cent of the added amounts.

MAXWELL

Langford, H. G., and Snively, J. R.: **Effect of DCA on Development of Renoprival Hypertension.** *Am. J. Physiol.* 196: 449 (Feb.), 1959.

The administration of desoxycorticosterone acetate (DCA) to nephrectomized dogs drinking 1 per cent saline accelerated the development of hypertension. In nephrectomized rats given 0.9 per cent saline intraperitoneally it was shown that this hypertension was not due to increased sodium intake or dehydration.

KAYDEN

Fraser, B. N.: **Manifestations and Aetiology of Hypertension in the Coloured and Bantu.** *Brit. M. J.* 1: 761 (Mar. 21), 1959.

This study was undertaken to clarify conflicting reports on the incidence, etiology, morbidity, and mortality from hypertension in the Bantu and the Coloured. The data indicated that hypertension and its complications were a common cause for hospital admission in Johannesburg and that these cases carried a high mortality. Females were more commonly afflicted than males. Renal disease was a common underlying cause. Compared with the European, hypertension presented at a similar age, but was more serious in the female, and the cause of death was more evenly distributed between heart failure, cerebrovascular accidents, and uremia. Endocrine causes of hypertension were rare. Electrocardiographic changes commonly showed evidence of left ventricular hypertrophy, even among the milder cases, and perhaps malnutrition was partially responsible for this.

KRAUSE

METABOLIC EFFECTS ON CIRCULATION

Highman, B., Maling, H. M., and Thompson, E. C.: **Serum Transaminase and Alkaline Phosphatase Levels After Large Doses of Norepinephrine and Epinephrine in Dogs.** *Am. J. Physiol.* 196: 436 (Feb.), 1959.

An intravenous infusion in conscious dogs of a large dose of norepinephrine (0.51-0.85 mg./

Kg.) or epinephrine (0.55-0.92 mg./Kg.) resulted in an elevation in serum glutamic oxalacetic transaminase (SGO-T), which reached a peak in about 6 hours and subsided within 2 to 3 days. Serum glutamic pyruvic transaminase (SGP-T) and serum alkaline phosphatase increased more gradually and subsided more slowly. Pathologic studies confirmed the myocardial and hepatic damage suggested by the elevated serum enzyme levels. Subcutaneous injection of 1 mg./Kg. of epinephrine-in-oil produced less severe pathologic changes, but resulted in a gradual increase during the first day in SGO-T, SGP-T and serum alkaline phosphatase with peak levels considerably higher than those following the intravenous infusions. Markedly elevated serum enzyme levels, suggesting cellular damage with altered permeability, occurred even in animals showing no significant myocardial hypersensitivity and no significant myocardial and hepatic changes demonstrable by the usual histologic methods. Dibenzylamine, an adrenergic blocking agent, prevented the rise in serum transaminase but not the rise in serum alkaline phosphatase.

KAYDEN

PHARMACOLOGY

Millar, R. A., Keener, E. B., and Benfey, B. G.: Plasma Adrenalin and Noradrenalin after Phenoxybenzamine Administration, and During Hemorrhagic Hypotension, in Normal and Adrenalectomized Dogs. Brit. J. Pharmacol. 14: 9 (Mar.), 1959.

The intravenous administration of phenoxybenzamine (Dibenzylamine) to lightly anesthetized dogs markedly raised the arterial epinephrine and norepinephrine concentrations, an effect which was heightened by hemorrhagic hypotension. Under the same test conditions, adrenalectomized dogs showed rises only in norepinephrine concentration. It appeared that phenoxybenzamine induced the release of epinephrine from the adrenal gland and that at least part of the norepinephrine rise was of extra-adrenal origin.

ROGERS

Benfey, B. G., Ledoux, G., and Melville, K. I.: Increased Urinary Excretion of Adrenalin and Noradrenalin after Phenoxybenzamine. Brit. J. Pharmacol. 14: 142 (Mar.), 1959.

The intravenous injection of phenoxybenzamine hydrochloride (Dibenzylamine) into anesthetized dogs was followed by hypotension and by a marked increase in urinary epinephrine and norepinephrine excretion. Both effects were prevented by pretreatment with hexamethonium. Metacholine-induced hypotension produced a

moderate increase in urinary epinephrine output but no change in norepinephrine. Acetylcholine induced diuresis of epinephrine was unaffected by phenoxybenzamine but that of norepinephrine was increased. During infusion of epinephrine or norepinephrine, phenoxybenzamine increased the excretion of both amines. It was thought that phenoxybenzamine increased epinephrine output by stimulating the adrenal gland, at least partly by producing hypotension; the increased norepinephrine output was otherwise unexplained.

ROGERS

Iowenthal, J., and Taylor, J. D.: A Method for Measuring the Activity of Compounds with an Activity Like Vitamin K against Indirect Anti-coagulants in Rats. Brit. J. Pharmacol. 14: 1 (Mar.), 1959.

Since the assay of vitamin K in the vitamin-deficient chick estimates dietary activity, the present method was developed to estimate anti-prothrombinopenic effect. Rats were fed warfarin until the prothrombin time was increased tenfold. Then various vitamin K products were administered and their effect estimated by a "bed-side" prothrombin test and a micromethod proconvertin determination. A specially processed vitamin K₁ preparation produced an optimal effect within 30 minutes. Two proprietary K₁ preparations were considerably less active, while vitamin K₃ and its water-soluble analogues in large doses showed no activity after 2 hours. Statistical analyses of the results are presented.

ROGERS

Brill, I. C., Krueger, J. D., and McCawley, E. L.: Restoration of Sinus Rhythm in Experimental and Clinical Ventricular Arrhythmias by Methoxamine Hydrochloride. Am. J. Cardiol. 3: 307 (Mar.), 1959.

Ventricular premature beats or tachycardia was induced in dogs by ligation of a coronary artery, by injecting zinc hydroxide solution into the myocardium, by administering digitalis, or by infusing amodiaquin. In each case, intravenous or intramuscular methoxamine (Vasoxyl) 0.5 to 1 mg. per Kg. promptly suppressed the arrhythmia for periods up to 60 minutes. Similar results were obtained when 5 to 25 mg. of methoxamine in 5 per cent dextrose solution was given to 14 patients having ventricular arrhythmia due to various types of heart disease with or without hypotension. The antiarrhythmic effect of the drug in some instances was achieved without a pressor effect.

ROGERS

Matuchni, J., King, W., and Resinski, M.: Hydrochlorothiazide, a New Saluretic. *Am. J. M. Sc.* 237: 479 (April), 1959.

Clinical and biochemical observations are recorded on 15 patients following the oral administration of hydrochlorothiazide. The dosage was usually 50 mg. 4 times daily. The dietary sodium was limited to 200 mg. daily. The drug was well tolerated. There was a marked increase in excretion of sodium and chloride which began as early as 1 hour and reached a peak in 3 to 4 hours following the administration of the drug. One patient developed significant hyponatremia and hypochloremia associated with weakness. In further instance significant hypopotassemia was produced. These changes were temporary. Potassium excretion was only slightly increased. The amount of diuresis and consequent weight loss varied with the degree of preexisting edema. Hydrochlorothiazide was antihypertensive in patients with an elevated blood pressure. One patient developed a temporary asymptomatic hyperuricemia. These observations confirm the use of hydrochlorothiazide as a potent well-tolerated saluretic drug.

SHEPS

Wasserman, F., Brodsky, L., Kathe, J. H., Rodensky, P. L., Dick, M. M., and Denton, P. S.: The Effect of Molar Sodium Lactate in Quinidine Intoxication: An Experimental Study. *Am. J. Cardiol.* 3: 294 (Mar.), 1959.

Quinidine hydrochloride administered intravenously to dogs in doses of 30 to 37 mg. per Kg. produced the following changes, which were spontaneously reversible within 35 minutes: prolongation of P-R and QRS intervals, S-T depression, slowing of heart rate, and moderate lowering of blood pressure. The intravenous administration of 20 to 180 ml. of molar sodium lactate solution gradually corrected these quinidine effects beginning within 2 minutes and ending in 20 minutes. Larger doses of quinidine produced sinoatrial arrest, atrioventricular nodal rhythm, hypotension, and finally ventricular fibrillation or arrest. Lactate therapy partially reversed some of these changes but only temporarily. The possible mechanisms of these phenomena are discussed.

ROGERS

PHYSIOLOGY

de Veen, H. H., Schatman, B., and Moskowitz, H.: Effect of Digitalis on Potassium Toxicity in Isolated Turtle Heart. *Proc. Soc. Exper. Biol. & Med.* 100: 538 (Mar.), 1959.

Potassium administration can antagonize the toxic effects of digitalis. Patients receiving digitalis may exhibit digitalis toxicity when their

potassium intake is restricted and over-digitalized patients may respond successfully to potassium administration. The experiments reported were designed to determine whether digitalis could antagonize the effects of potassium toxicity on the myocardium. Accordingly, potassium-enriched solutions were used to perfuse 30 isolated turtle hearts; this caused diminished strength of isometric contractions. This decrease in strength of contraction was progressive with increasing concentration of potassium until generally asystole occurred. Digitalis did not protect against the development of asystole, but did sustain the strength of myocardial contraction.

KRAUSE

Gerola, A., Feinberg, H., and Katz, L. N.: Role of Catecholamines on Energetics of the Heart and Its Blood Supply. *Am. J. Physiol.* 196: 394 (Feb.), 1959.

Open-chest anesthetized dogs were prepared for measurement of total coronary flow and myocardial oxygen consumption. The effects of continuously infused intravenous l-pinephrine and l-norepinephrine (5 gamma/Kg./min.) were determined and compared with control values. When catecholamines were infused at any fixed cardiac output, cardiac oxygen consumption rose in association with increases in blood pressure and heart rate, while cardiac external mechanical efficiency declined. The product of mean blood pressure and heart rate have consistently correlated with myocardial oxygen consumption over a wide range of cardiac output, blood pressure, and heart rate. The significance of this value was considered also in view of the changes brought about by catecholamines in this relationship. The decline in the coronary arteriovenous oxygen difference, the percentage of oxygen extracted by the heart, and the rise in coronary venous oxygen, were all attributed to a direct action of catecholamines on the coronary vessels. Despite their new levels, the coronary venous content oxygen, and the coronary arteriovenous oxygen differences remained fairly constant as the cardiac effort and its oxygen requirement varied during catecholamine infusion.

KAYDEN

de Mello, W. C.: Metabolism and Electrical Activity of the Heart: Action of 2,4-dinitrophenol and ATP. *Am. J. Physiol.* 196: 377 (Feb.), 1959.

The effects of dinitrophenol (DNP) on the electrical activity of single cells of the sinus node, right atrium, and atrioventricular node, were studied with microelectrodes in rabbits. The drug caused an initial tachycardia followed

by a bradycardia, a decrease in the duration of the action potential, a decrease of the resting potential, and a decrease in the slope of diastolic depolarization of pacemaker tissues. A complete inhibition of the electrical activity was observed in 45 minutes after the addition of DNP to the perfusion fluid. A significant recovery of the electrical activity was obtained with the use of a system with DNP and ATP (adenosine triphosphate). The incomplete loss of the resting potential noted with DNP suggested that at least a fraction of the resting potential was independent of the energy supplied by oxidative phosphorylation.

KAYDEN

Glaser, W., and Brandt, J. L.: Localization of Magnesium-28 in the Myocardium. *Am. J. Physiol.* 196: 375 (Feb.), 1959.

The concentration of magnesium-28 in heart muscle is greater than in skeletal muscle. The interventricular septum was found to have an even greater ability to concentrate magnesium-28 compared to the right and left ventricular walls. The analysis of the isolated Purkinje system in 2 calves made it unlikely that the distribution of this specialized tissue was the explanation for the distribution of magnesium-28 in the different portions of the ventricles.

KAYDEN

Bullard, R. W.: Cardiac Output of the Hypothermic Rat. *Am. J. Physiol.* 196: 415 (Feb.), 1959.

As the colonic temperature of the rat was lowered, the heart rate and cardiac output fell linearly with the temperature. The arterial pressure did not fall linearly, indicating an increase of total peripheral resistance. The increase of hematocrit ratio and the effect of cold on blood per se combined to increase the in vitro viscosity threefold as the colonic temperature approached 15 C. It appears from these data that the increase in viscosity of the blood is the important factor in the increase in total resistance to flow.

KAYDEN

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Selye, H., and Bajusz, E.: Effect of Various Electrolytes Upon Cardiac and Skeletal Musculature. *Brit. J. Pharmacol.* 14: 83 (Mar.), 1959.

Sodium salts (NaClO_4 , Na_2SO_4 , Na_2HPO_4) administered by gavage frequently produced cardiac necroses in rats on a potassium-deficient diet, an effect previously noted in corticoid-treated animals. Severe muscular cramps also

occurred in those receiving the perchlorate and the phosphate salts. Both skeletal and cardiac muscular effects were prevented by concomitant administration of potassium chloride or, to lesser degree, of magnesium chloride. Neither cramps nor necroses were induced by gavage with comparable quantities of sodium chloride alone, indicating that the union was important in producing these muscular changes.

ROGERS

Blackmore, W. P.: Comparative Effects of Chlorothiazide and Mersalyl (Mersalyl Sodium and Theophylline) on the Kidney. *J. Pharmacol. & Exper. Therap.* 126: 303 (April), 1959.

This study evaluated the comparative effect of chlorothiazide and a mercurial diuretic (mersalyl sodium and theophylline) on osmolar clearance "free" water clearance, glomerular filtration rate, and renal excretion of sodium, potassium, and chloride. Each compound was given intravenously in a concentration sufficient to produce a marked diuretic response. Chlorothiazide had a more rapid onset of action than mersalyl. Chlorothiazide was an effective diuretic even in the presence of a significant decrease in glomerular filtration rate, indicating a direct tubular response. In moderately hydrated dogs, chlorothiazide produced no change in "free" water clearance and a moderate increase in osmolar clearance. Mersalyl increased "free" water clearance and greatly increased osmolar clearance. In dogs undergoing maximal water diuresis both diuretics produced a significant increase in osmolar clearance and no significant change in "free" water clearance.

RINZLER

Daniel, E. E., Dodd, A., and Hunt, J.: Effects of Pitressin and Isoproterenol on Aorta Electrolytes. *Arch. Int. Pharmacodyn.* 119: 43 (Mar.), 1959.

Isoproterenol (1 mg. per Kg.) and pitressin (0.1-1.0 unit per animal) were administered to rats. Variations in sodium concentration in the tissues of the aorta were studied and correlated with the blood pressure levels. The observed variations in aorta sodium support the theory recently proposed by others that during blood pressure changes, sodium ion moves into and out of vascular muscle cells. However, the changes were much too small to account for the shifts of sodium postulated by these workers. The authors propose the following working hypothesis: the rise in aorta sodium concentration and blood pressure represent an increase in intracellular sodium and aortic contraction is accompanied by depletion of potassium.

BRACHFELD

Woods, J. W.: Susceptibility of Rats with Hormonal Hypertension to Experimental Pyelonephritis. *J. Clin. Invest.* 37: 1686 (Dec.), 1958.

To test the hypothesis that experimental animals with hypertension and renal arteriolar disease may have an increased susceptibility to induced pyelonephritis, the author compared the incidence of pyelonephritis in a control group of unilaterally nephrectomized rats to which intravenous inoculations of *Escherichia coli* were given to the incidence in a similarly prepared group in which hypertension had been induced with desoxycorticosterone and saline prior to bacterial injection. The experimental hypertension was found to be characterized by diffuse arteriolar sclerosis and dilatation of the renal tubules. Microscopic and bacterial studies were performed on the remaining kidneys at the time of sacrifice of the animals, which varied from 2 to 15 days following bacterial injection except in those who appeared to be dying during the first 2 days following induced infection. The desoxycorticosterone and saline caused hypertension in about 2 weeks and soon thereafter vascular disease developed. In the first group studied 7 out of 12 hypertensive rats and none of the 12 control animals showed evidence of renal infection (defined as a colony count of greater than 1 million colonies per gram of kidney tissue). In a second group the number of bacteria injected was chosen so that it would not cause infection in a significant number of controls. Here, 16 to 21 hypertensive rats and only 3 of 21 control animals developed pyelonephritis, while 9 hypertensive animals had macroscopic abscesses, 2 had microscopic abscesses, and 3 had infiltrates of inflammatory cells. Two of the infected control animals had macroscopic abscesses. Other organs were not infected, and the difference between the incidence of pyelonephritis in the control and hypertensive groups was found to be statistically highly significant although the author believed that the study did not elucidate the nature of the factor or factors causing this difference.

FREEDBERG

Kirkendall, W. M., Culbertson, J. W., and Eckstein, J. W.: Renal Hemodynamics in Patients with Coarctation of the Aorta. *J. Lab. & Clin. Med.* 53: 6 (Jan.), 1959.

In 21 patients with coarctation of the aorta, 5 normotensive men, and 29 men with essential hypertension, measurements of effective renal plasma flow with sodium para-aminohipurate glomerular filtration rate by inulin or

sodium thiosulfate clearance, and brachial and femoral arterial pressure levels were made. Segmental renovascular resistance values were calculated from the formula of Gomez. When compared with normotensive patients, the coarctation group showed characteristic damping of the pressure pulse waves in the femoral artery, but a virtually identical mean blood pressure. The filtration fraction was increased in the coarctation group and there was a similar increase in the net efferent renal vascular resistance. All other measured functions were identical to the normal group. When compared with the male essential hypertensive patients, the patients with coarctation had a significantly lower brachial arterial diastolic pressure but comparable systolic and mean pressure levels. Femoral arterial pressure in all phases was very significantly lower in the coarctation group. Glomerular filtration rate and effective renal plasma flow were significantly higher in the coarctation group, while total renal vascular resistance was greatly increased in the essential hypertensive patients. A comparison between the normotensive and essential hypertensive groups showed significant differences in all renal hemodynamic functions tested except glomerular filtration rate. Four patients with coarctation and congestive heart failure were studied and found to have hemodynamic changes characteristic of patients with mild congestive heart failure from other causes with decreased effective renal plasma flow, normal glomerular filtration rate, high filtration fraction, and increased postglomerular renal vascular resistance. It is concluded by the authors that the data presented demonstrates that renal circulation in uncomplicated patients with coarctation of the aorta is essentially normal and that there is no evidence to support the view that there is generalized systemic arteriolar constriction in patients with coarctation of the aorta.

MAXWELL

RHEUMATIC FEVER

Saslaw, M. S., and Streifeld, M. M.: Group A Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Florida: I. Bacteriologic Observations from October 1954 through May 1955. *Dis. Chest* 37: 175 (Feb.) 1959.

Throat cultures were made at monthly intervals on 232 children ages 6 through 9 throughout the academic year in 2 schools in Miami, Florida. Similar throat cultures at random times throughout the study period were taken from 1,200 other children in the same age group in 48 other schools. Forty-five per cent of an average of 305

children harbored group A beta hemolytic streptococci at least once in the 8-month study period. Monthly isolation rates for the small and large groups were similar at approximately 14 per cent. A small but significant decrease in recovery of the streptococci was found with advance in age. Variation in recovery of group A beta hemolytic streptococci with sex was as follows: age 6 to 7, male greater than female; age 7 to 8, male equal to female; age 8 to 9, female greater than male.

MAXWELL

ROENTGENOLOGY

Fogel, M., Somogyi, Z., and Gacs, J.: Transposition of the Pulmonary Veins. *Fortschr. Roentgenstr.* 90: 32 (Jan.), 1959.

A 20-year-old woman showed in the regular frontal plane roentgenogram a right pulmonary vein leading to the inferior vena cava, at the junction between diaphragm and the right atrium; this vein was more clearly visualized by means of tomography and angiocardiology. Angiocardiology also disclosed a hypoplastic right pulmonary artery and an atrial septal defect. A bronchogram showed absence of the bronchi of the right middle lobe and hypoplastic bronchi of the lower lobe.

LEPESCHKIN

Schad, N., and Künzler, R.: Angiocardiographic Observations in Ventricular Septal Defect as an Isolated or Combined Anomaly. *Fortschr. Roentgenstr.* 90: 22 (Jan.), 1959.

After dye injection into the pulmonary artery through a catheter, late filling of the right ventricle from the left ventricle through the ventricular septal defect may be demonstrated by means of serial roentgenograms in 2 planes (especially in the lateral plane). In isolated septal defect this filling occurs in systole but in the presence of tricuspid atresia the filling occurs in diastole. Injection of dye into the right ventricle under pressure may produce a transient small right-to-left shunt in diastole. A pronounced shunt under these conditions, however, is suggestive of additional pulmonary stenosis, pulmonary hypertension, or dextroposition of the aorta. Tetralogy of Fallot is characterized by the appearance of a dense levogram with secondary filling of the pulmonary artery. If both aorta and pulmonary artery become visualized, greater dye concentration in the pulmonary artery suggests an Eisenmenger complex. A considerable difference in the systolic and diastolic diameters of the pulmonary artery suggests pulmonary hypertension.

LEPESCHKIN

Kunzler, R., and Schad, N.: Angiocardiographic Demonstration of Persistent Ductus Botalli. *Fortschr. Roentgenstr.* 90: 14 (Jan.), 1959.

Serial angiocardiography of the persistent ductus arteriosus can be of help when this cannot be catheterized directly or when other anomalies are suspected. Injection of dye through the catheter into the pulmonary artery rather than into the right ventricle results more easily in visualization of the ductus, which usually becomes filled in diastole because of increased pulmonary artery pressure as a result of the injection. The ascending aorta remains free of dye, and this makes it possible to rule out aorticopulmonary communication. Sometimes the ductus may become filled from the aorta later late filling of the pulmonary artery is indirect proof of patency. Another indirect proof is localized or diffused dye dilution in the pulmonary artery near the ductus, which appears usually in late diastole. When the pulmonary artery shows late filling through the ductus, systolic dye dilution from the right ventricle can be observed.

LEPESCHKIN

Smid, J.: Unusual Roentgenological findings in Cardiac Thrombus. *Fortschr. Roentgenstr.* 90: 38 (Jan.), 1959.

A 14-year-old girl showed during fluoroscopy a heavily calcified body in the region of the right atrium, showing a circular vibratory movement to the left with every heart beat. An operation, carried out on the basis of the roentgenologic diagnosis, disclosed a calcified free thrombus the size of a nut, attached to the wall of the right atrium near the dorsolateral insertion of the inferior vena cava by means of a narrow pedicle.

LEPESCHKIN

Davies, P., and Bucky, N. L.: Tomography of Calcified Aortic and Mitral Valves. *Brit. Heart J.* 21: 17 (Jan.), 1959.

The radiologic demonstration of calcified aortic and mitral valves has assumed prognostic importance with the advent of valvotomy. The authors reviewed their experience with tomography and fluoroscopy in 20 patients with aortic valve calcification and 15 patients with mitral valve calcification. They concluded that tomography was more reliable than fluoroscopy, since with tomography calcification was detected more frequently and its site located with more certainty. The form of the calcification was useful in distinguishing each valve, since aortic valve calcification took the form of a channel or ring and mitral valve calcification usually resembled an irregular star.

PAUL

SURGERY AND CARDIOVASCULAR DISEASE

eland, W. P., Beard, A. J. W., Bentall, H. H., Bishop, M. B., Braimbridge, M. V., Bromley, L. L., Goodwin, J. F., Hollman, A., Kerr, W. F., Lloyd-Jones, E. B., Melrose, D. G., and Telivuo, L. J.: *Treatment of Ventricular Septal Defect*. *Brit. M. J.* 2: 1369 (Dec. 6), 1958.

This operative group consisted of 21 patients with ventricular septal defects corrected by open-heart surgery using extracorporeal circulation. The clinical features, cardiac catheterization data, surgical technique, and operative results were reviewed. Of the 15 patients with a ventricular septal defect as the sole lesion only 1 died. The main hazard with closure was the presence of severe pulmonary vascular disease. If the pulmonary resistance was high enough to cause an obvious right-to-left shunt with an arterial oxygen saturation below 85 per cent with or without cyanosis or clubbing, then closure of the ventricular septal defect was contraindicated. The most important associated defect was a patent ductus for it rendered perfusion impossible. Therefore, if this lesion was suspected to coexist with the septal defect, retrograde aortography had to be accomplished before surgical correction of the septal defect was undertaken.

KRAUSE

Krauss, H., Musshoff, K., Frisch, P., Reindell, H., and Klepzig, H.: *Cardiovascular Changes after Ligation of a Patent Ductus Arteriosus*. *German M. Monthly* 3: 371 (Dec.), 1959.

In 13 patients with patent ductus arteriosus followed postoperatively for as long as 5 years, the preoperative and postoperative radiographic findings were compared with clinical and laboratory examination. Because of the marked circulatory instability the radiographic examinations with the patient upright gave a false picture after operation. Cardiac volume (as determined from the films with the patient lying down) was found to be greater among patients with associated pulmonary hypertension. Postoperatively the cardiac volume consistently diminished with the maximum diminution being found after about 9 months. This suggested that reoperative enlargement of the left heart in cases of patent ductus arteriosus without pulmonary hypertension was caused by an increase in residual blood volume—a compensatory cardiac enlargement. The enlargement of the right atrium and right ventricle among patients with associated pulmonary hypertension was considered to be due to myogenic dilatation with latent

cardiac insufficiency. Continued observation postoperatively showed recurrence of cardiac enlargement after the initial diminution in heart size, but at a size below the preoperative level in all instances. With associated pulmonary hypertension the heart remained enlarged beyond normal limits; in the group with uncomplicated patent ductus arteriosus the increased heart size was still within the normal limits of cardiac volume relative to body weight. These results indicate that surgical closure of a patent ductus arteriosus should be performed before pulmonary hypertension has developed.

SAGALL

Campbell, M.: *Late Results of Operations for Fallot's Tetralogy*. *Brit. M. J.* 2: 1175 (Nov. 15), 1958.

The author describes his experience with the results of operation in the tetralogy of Fallot. The operative procedures primarily used were: subclavian pulmonary anastomosis or a modification of this, and Brock's direct operations of pulmonary valvotomy or infundibular resection or both. Good results were maintained in 80 per cent after anastomotic and in 89 per cent after direct operations. The long-term advantage of the direct operation was particularly evident for only one half as many deaths occurred and half as many lost all their improvement in the group who underwent the direct operation when compared to the anastomotic group. When improvement was lost after a good postoperative result several factors were responsible. First of all the patient still was left with a tetralogy, though the stenosis had been to some extent relieved, directly or indirectly. Cerebral complications were responsible for more than a third of the deaths; the heart could not support the increased pulmonary flow and the increased activity that it allowed in another third; but in the final third the cause was not directly related to the heart condition or the operation. In many patients who lost their improvement after anastomosis, the deterioration was due to closure of the anastomosis. In others, after either operation, the loss of improvement was due to the stenosis progressing. After anastomosis, increasing difficulty in hearing a continuous murmur was a bad sign and usually meant that the anastomosis was closing. The auscultatory signs after the direct operation were not as helpful. Usually the heart increased in size within a few weeks after a successful operation. On the average, the cardiothoracic ratio increased by one tenth (49 to 54 per cent) and remained at this level for 8 to 10 years. There were no drawbacks to some increase in the size of the smaller hearts, generally about 10 per cent.

The goal was a limited increase, large enough to indicate a reasonable pulmonary blood flow that would permit the patient more activity, but not large enough to throw undue strain on the heart. Neither of these procedures is curative, for of course the ventricular septal defect remains and the right ventricle is working against the systemic pressure. There is reason to anticipate. Cutting these arteries may compromise the supply of the distal septal myocardium, as well as even better results with the open operation and closure of the ventricular septal defect and relief of the stenosis.

KRAUSE

Szilagyi, D. E., France, L. C., Smith, R. F. and Whitcomb, J. G.: The Clinical Use of an Elastic Dacron Prosthesis. Arch. Surg. 77:538 (Oct.), 1958.

This report describes the use of an arterial prosthesis manufactured from Dacron yarn woven in such a manner that the most important quality of elasticity is retained and the resulting tube elongates and flexes without deformity. Arterial bypasses were placed between the upper thoracic and lower abdominal aortas of 21 dogs; and in 10 such animals autopsied up to 9 months following surgery, the prosthesis was found to be intact. On specimens removed up to 3 months following insertion, the pseudointima appeared patchy although prostheses studied after this period of time had developed a smooth and intact pseudointima. Microscopically, almost a complete lack of cellular exudation was seen around the implants; and most significantly when compared to stretch Nylon, which showed poor durability, the tensile strength of the graft remained unchanged during the 9-month period. Eleven of the animals were alive with functioning prostheses between 5 and 11 months following surgery. In discussing the surgical technique involved in inserting the prosthesis, the authors stress the necessity of minimally coating the Dacron tube with blood to prevent excessive oozing, heat sealing the end of the prosthesis to prevent unraveling and very gently handling the fabric to obviate separation of threads. In 43 clinical cases Dacron grafts were used in the aortoiliac and femoral-popliteal areas and although the results were slightly inferior to those in which homografts were used (80 per cent of the Dacron group were patent at the time of the last examination), the authors believed that the difference in results was largely due to the fact that the arterial disease in the cases in which the synthetic was used was more advanced and diffuse. They point out that the advantage of the plastic prosthesis

should become apparent when the results are viewed in the long term, since deterioration should be significantly less.

FREEDBERG

James, T. H., and Burch, G. E.: Topography of the Human Coronary Arteries in Relation to Cardiac Surgery. J. Thoracic Surg. 36: 656 (Nov.), 1958.

Seventy human hearts were studied by injection of Vinylite into the coronary arteries, followed by hydrochloric acid corrosion. This provided a spatially oriented preparation of the heart chambers and vessels. In 4 different surgical procedures the above method was used to demonstrate the topography of the coronary arteries and how by disturbance of blood supply in these instances arrhythmias and conduction defects may develop. The first is the purse-string repair for mitral insufficiency. In this instance the blood supply to the sinoatrial node may be occluded when the suture is passed into the right atrium. In 60 per cent the SA nodal artery arises from the right coronary and in the other 40 per cent from the proximal portion of the left coronary artery. Consequences of occlusion of this vessel may be sinus arrest, atrial fibrillation, or other atrial arrhythmias. Posteriorly there are 2 hazards where the suture is passed out below the A-V valves. First, the artery to the AV node which in this study arose from the right coronary may be occluded. Consequences of this may be complete or incomplete atrioventricular block. Second, the posterior descending coronary artery which is not visible on the surface may be occluded with possible consequences of a posterior myocardial infarction. The second surgical technique is circumclusion closure for atrial septal defect. The necessary cleavage of the upper interatrial septum will almost certainly compromise the blood supply to the SA node. This artery is also endangered anteriorly when the circumclusion suture is passed into the base of the interatrial septum. Posteriorly the posterior descending coronary artery and the artery to the AV node may be jeopardized. Bleeding in the lower interatrial septum may occur from thin-walled Thebesian veins and sinuses in the loose areolar tissue in this area. Third, in regard to cannulation of the venae cavae for total cardiac bypass, the blood supply to the SA node may be disturbed by the tape securing the superior vena caval cannula. Fourth, in right ventriculotomy the upper end of the incision is near the pulmonary valve ring where there is an arterial circle connecting the proximal right and left coronary arteries as the bundle branches of the conducting system.

LEVINSON

Wall, R. A., Long, D. M., Gemmill, S. J., Lillehei, C. W.: **Certain Blood Changes in Patients Undergoing Extracorporeal Circulation.** *J. Thoracic Surg.* 37: 323 (Mar.), 1959.

The perfusion records of 350 cases of clinical cardiopulmonary bypass procedures, using helix reservoir bubble oxygenator and sigmamotor pump, were analyzed. The changes induced were a general a function of time. The cyanotic patients had a mean duration of perfusion time of 6 minutes and the acyanotic patients 27.5 minutes. Analyses were made of plasma hemoglobin, cardiomy loss, post-operative red blood cell survival, platelet counts and arterial pH. The rate of plasma hemoglobin formation in the cyanotic and acyanotic patients was about the same. In all of the patients the final plasma hemoglobin values were below that likely to cause any harm. No ill effects were observed. A decrease in platelet counts occurred immediately with return to normal in a few days. No bleeding could be attributed to a defect in the clotting mechanism but rather to defective hemostasis. The bleeding problems in the post perfusion period could usually be traced to inadequately cleaned and sterilized perfusion equipment, blood incompatibilities, or inadequate hemostasis. Mild decreases in the patient's hemoglobin were noted in the post-operative period. This was attributed to hemodilution with resumption of oral intake of fluid. Significant changes in pH were not noted by setting the arterial pump at 50 to 100 ml. per Kg. of body weight per minute. It is recommended to start at lower levels with increase of arterial output of the pump as necessary to maintain normal electroencephalograms and mean systemic blood pressures.

LEVINSON

Helmsthorpe, J. A., Kaplan, S., Clarke, L. C., Jr., McAdams, A. J., Matthews, E. C., and Edwards, E. C.: **Myocardial Injury Associated with Asystole Induced with Potassium Citrate.** *Ann. Surg.* 149: 200 (Feb.), 1959.

This report is concerned with the untoward effects of producing asystole with the Melrose technique, employing potassium citrate, in an extracorporeal oxygenation and circulation. Three groups of dogs were used. In the first group of 5, total cardiac bypass was used for 30 minutes with no mortality. In the second group of 17 dogs, the hearts were arrested with potassium citrate. In these experiments, there was incomplete drainage of blood from the left side of the heart during the 30-minute period of cardiac arrest and total bypass. In this group, there was a mortality of 50 per cent. The third group was a duplication of the second except that there was

complete drainage of blood from the left side of the heart. There was a loss of 1 dog in this latter group due to an accidental aortic tear which could not be repaired. This striking difference in mortality between the first and third groups on the 1 hand and the second group on the other, suggested that drainage of blood from the left atrium had a very beneficial effect upon cardiac function during this type of perfusion. The reason for this may lie in prevention of distention of pulmonary veins and removal of large concentrations of potassium from the left atrium. In the first group, the hearts were examined microscopically in 3 dogs 48 hours after total bypass. Changes consisted of occasional focal necrosis and some fatty degeneration. In a second group, where arrest was produced by anoxia resulting from 30 minutes of occlusion of the aorta just above the coronary ostia, focal myocardial hemorrhage was noted early. Other changes were fatty degeneration and some focal necrosis. The third group studied histologically were from dogs arrested with potassium citrate and with the left heart drained completely. These animals were sacrificed 48 hours after perfusion. In addition to visible gross lesions, all specimens showed microscopically extensive focal areas of myocardial necrosis. Thus, the impression, gained from survival rate, that drainage of the left side of the heart was associated with absence of myocardial changes in the potassium arrested hearts, was not confirmed by the microscopic findings.

LEVINSON

Collins, H. A., Harberg, F. J., Soltero, L. R., McNamara, D. G., Cooley, D. A.: **Cardiac Surgery in the Newborn.** *Surgery* 45: 506 (Mar.), 1959.

One hundred and twenty infants under the age of 1 year were operated upon for congenital malformations of the heart or great vessels on an emergency or semi-emergency basis because of severe cardiac decompensation or anoxemia. Thirteen infants were under the age of 1 month, and 9 survived. In 38 infants the operation necessitated the use of a pump oxygenator for temporary cardiopulmonary bypass. Eighty-three or 69 per cent of the infants survived operation and were improved. Twenty-nine infants with ventricular septal defect were operated upon using temporary cardiopulmonary bypass. Forty-one per cent of the infants died following closure of the defect. This mortality rate is 6 times that of the same procedure in patients over the age of 2. Because of this, surgical therapy should be postponed until after the age of 2 if at all possible. Twenty-eight infants with a provisional diagnosis of tetralogy of Fallot were operated

upon and anastomotic procedures carried out. The immediate mortality was 21 per cent. The survivors nearly all had immediate and striking improvement. Because the anastomosis may not increase in size with the growth of the infant, it is possible to interrupt the anastomosis and perform direct repair if the infant gets into difficulty at a later age. Severe cardiac decompensation due to coarctation of the aorta necessitated operation in 14 infants under the age of 1 year. The coarctation was of the preductal type in 4 infants and these all died. The remainder had postductal coarctation and did well. Patent ductus arteriosus was found at operation in association with coarctation in all patients. Nine infants with patent ductus arteriosus in whom cardiac failure was of sufficient severity to justify closure of the ductus were operated upon. Three died in the postoperative period. Five of the survivors were greatly benefited while the sixth improved only moderately. The latter had a ventricular septal defect. In infants with an additional left to right shunt at the atrial or ventricular level, interruption of a patent ductus may result in sufficient improvement to allow delay of the definitive intracardiac procedure. In addition the experience with transposition of the great vessels, tricuspid atresia, aortic stenosis, pulmonic stenosis, and anomalous pulmonary venous drainage was reviewed. A decision to operate on all of these patients was based on the impression that survival was not possible otherwise.

SHEPS

Dale, W. A., and Mavor, G. E.: Peripheral Vascular Grafts. *Brit. J. Surg.* 66: 305 (Jan.), 1959.

Autogenous vein, homologous artery, and synthetic heterografts were used as peripheral shunt arteriografts in dogs. Arteriografts were subsequently done in intervals and postmortem examination of the grafts done when the arteriogram showed occlusion of the graft, or at a predetermined time if the graft remained patent. Sixteen of 42 (36 per cent) vein grafts thrombosed prior to sacrifice. These were end-to-side femoral or ileo-femoral. The majority of the thromboses occurred in the first few dogs. Fourteen of 43 (23 per cent) homografts were thrombosed. These were placed in the same location. Forty-eight of 68 (71 per cent) of the synthetic grafts using 5 different materials thrombosed. Microscopic examination revealed that the autogenous veins consisted of living tissue with fibrous thickening of all layers, while homografts became fibrous tubes with broken elastic fibers encased in the smooth muscle layer but with no

thickening of the wall. The synthetics were noted for the thickness of the neo-intima, which was thought to enhance thrombosis. The absence of an aneurysmal dilatation of autogenous veins was mentioned, and an explanation attempted in terms of the La Plae's law.

MAXWELL

MacLean, L. D., Phibbs, C. M., Flom, R. D., and Brainard, J. B.: Replacement of Vital Veins *Ann. Surg.* 149: 549 (April), 1959.

There is need for replacement or bypass of vital veins in portal hypertension, malignancy trauma, superior vena cava syndrome and in congenital heart disease where there is total anomalous pulmonary venous drainage or high interatrial septal defect with anomalous pulmonary venous drainage to the superior vena cava. Most of this work has been done in dogs. Aortic homografts, synthetics and venous autografts have usually resulted in constriction in short periods of time. These authors in a previous report had used Ivalon as a prosthesis with resultant constriction or complete obstruction of the grafts in all instances. In the present report they employed aortic homografts in 11 dogs. Of these, 7 had constriction or complete obstruction of the graft. In 13 dogs Ivalon in 2 layers with Lucite rings between them was used as a graft. Of these only 4 had constriction or obstruction. It is pointed out that in 3 of these the obstruction or constriction occurred at the end of the graft where a Lucite ring had not been included in the sutures. It is felt that the relative success of the Ivalon-Lucite graft is due to the fact that this graft does not collapse in the presence of the relatively low pressure in the veins. The latter is thought to be the cause for failure of the other types of grafts. It was interesting that in 1 of the dogs, where complete obstruction of the graft occurred, that the large collateral channel that developed did not prevent ascites although the dog lived for 10 months. This collateral was well demonstrated on a venogram. After 10 months 9 of the original 13 dogs with Ivalon-Lucite grafts were alive and free of obstruction or ascites. Only 3 of the 11 dogs with aortic homografts were alive at the end of 10 months and 1 of these had ascites.

LEVINSON

Henly, W. S., Crawford, E. S., De Baakey, M. E., and Halpert, B.: The Fate of Equine-to-Canine Arterial Heterografts. *Arch. Pathol.* 67: 264 (Mar.), 1959.

Fifteen fresh equine common carotid arteries were lyophilized and subsequently reconstituted by immersing the arteries in isotonic saline solu-

tion until soft and pliable. These arteries were then grafted into the abdominal aortas of 15 mongrel dogs replacing a segment of the aorta 3 cm. long between the renal arteries and the bifurcation. Two of the heterografts were removed after 15 days; 2 after 60 days; and the remainder after 15 months. The 2 grafts examined 15 days after placement showed good healing along the suture lines and no significant growth change in the walls of the grafts. In the 2 removed after 60 days there was slight dilatation of the grafts. The graft lumen was one-fourth more spacious than that of the proximal and distal portions of the aorta. Of the 11 grafts left in place for 15 months, 1 was completely occluded by a thrombus and in the others there was aneurysmal dilatation of varying degrees so that in some instances the lumen was almost tripled. Microscopic examination revealed that the host tissue had apparently completely replaced the graft. Examination of the lyophilized equine common carotid artery revealed serious damage to the muscular media by the lyophilizing process. It was concluded that the injury weakened the wall and thereby resulted in the dilatation.

MAXWELL

Harrison, J. H.: **Synthetic Materials as Vascular Prostheses. III. Long Term Studies on Grafts of Nylon, Dacron, Orlon, and Teflon Replacing Large Blood Vessels.** Surg., Gynec. & Obst. 108: 433 (Apr.), 1959.

Previous observations of synthetic thoracic aortic grafts in 84 dogs over periods up to 2 years had shown that those of Ivalon sponge deteriorated rapidly leading to aneurysm and rupture, that Nylon grafts lost 80 per cent of their strength by 6 months and up to 95 per cent after 2 years, and that grafts of Orlon, Dacron or Teflon lost little strength after 1 year. The present report describes the status of the grafts in 10 dogs 2 to 3 years after their placement. All grafts were patent. Two Nylon grafts ruptured while 1 Nylon graft, and 2 each of Orlon and Dacron presented hematomas from delayed bleedings. One Nylon graft and 2 Teflon grafts had healed well. Therefore, Teflon was considered to be the synthetic material of choice and superior to homografts for replacing vessels larger than 9 mm. in diameter.

ROGERS

UNCOMMON FORMS OF HEART DISEASE

Nichols, J., and Henningar, G.: **A Case of Bilateral Multicentric Cardiac Myxoma.** Arch. Path. 67: 24 (Jan.), 1959.

The paper consists of a case presentation of a 19-year-old woman, with a history suggestive of acute rheumatic fever 24 months prior to death. Symptoms suggestive of a left cerebral embolus occurred 18 months before death, and thereafter she followed a nonremitting downhill course with symptoms of rheumatic heart disease and the eventual development of atrial fibrillation. The patient died after an embolectomy, which was necessitated by development of arterial occlusion in both lower extremities following attempted left atrial catheterization. Autopsy revealed multicentric bilateral cardiac myxoma. All pedicles of all the tumors were continuous with the fibrous tissue of the limbus of the foramen ovale. There were in addition old and recent infarcts of the kidney, spleen, lungs, and brain. There was no evidence of there ever having been a rheumatic episode except for the finding of an interstitial myocarditis. The pathogenesis of cardiac myxomas is discussed, and the authors conclude that cardiac myxomas are true neoplasms arising without relation to prior thrombi.

MAXWELL

Isaacs, J. P.: **Sixty Penetrating Wounds of the Heart.** Surgery 45: 696 (April), 1959.

Of 133 patients with penetrating wounds of the heart, 60 arrived alive at the hospital and were treated, with a mortality of 16.7 per cent. The remaining 73 persons were dead on arrival. The majority of the injuries were by stabbing. Acute pericardial tamponade or severe extrapericardial hemorrhage was the most frequent complication. Mortality was greater with extrapericardial hemorrhage alone than with tamponade alone. Either a ventricle or great arterial vessel was penetrated in nearly all the fatal cases. Other complications included lesions such as laceration of coronary arteries with myocardial infarction, damage to intracardiac or great vessel valves, or division of the conduction system. Two patients of the group with tamponade treated nonoperatively developed chronic constrictive pericarditis requiring decortication. Experimental observations were quoted which demonstrated an exponential relationship between pericardial volume and pericardial pressure. The rising pericardial pressure acts as an external pressure counteracting that of the intraventricular venous filling pressure in diastole. The ventricular chambers inside the pericardium can then fill only very little as the cost of very high filling pressures. The circulation ceases at the maximal static pressure which the over-all circulatory system is capable of reaching without its ventricular pumps. This pressure is 17 cm. of water on the

average, given a normal blood volume. Given a greater or lesser blood volume the value of pericardial pressure at which the circulation of blood ceases is somewhat higher or lower accordingly. At any level of mild to moderate tamponade, an increase in blood volume definitely raises aortic pressure and cardiac output, but does little at levels of severe tamponade. Similarly, sympathomimetic amines administered during tamponade produce some hemodynamic benefit by augmenting myocardial contractility and peripheral vascular smooth muscle tone. The most efficacious treatment of acute cardiac tamponade as implied from these experimental studies is pericardial aspiration, intravenous blood volume expanders, and intravenous or intracardiac stimulants. In some cases thoracotomy for evacuation of the pericardium and suture of the cardiac wound may be necessary. Operative treatment should be quickly resorted to for the more serious complication of severe extrapericardial hemorrhage, and those instances when the initial non-operative treatments are proved inadequate for definitive therapy. The low incidence of chronic constrictive pericarditis following the management of acute tamponade by pericardial aspiration alone is not great enough to contraindicate the use of non-operative therapy.

SHEPS

Sirak, H. D., Hosier, D. M., and Clatworthy, H. W., Jr.: Defects of the Interventricular Septum in Infancy: A Two-Stage Approach to Their Surgical Correction. *New England J. Med.* 260: 147 (Jan. 22), 1959.

The authors propose a 2-stage approach to the surgical correction of interventricular septal defects in infancy and report the first patient to be successfully treated by this method. The first stage of the procedure was performed in infancy and consisted of narrowing of the pulmonary artery by a band of plastic cloth. This maneuver increased the right ventricular outflow resistance, thereby reducing the left-to-right shunt across the ventricle. Thus the work of the left ventricle was decreased, the systemic circulation was improved and the lung vasculature was spared. After the child had grown large enough to tolerate open heart surgery, a corrective repair was performed as the second stage. At this time the septal defect was closed and the constriction removed from the pulmonary artery. By this approach it may be possible to increase both the immediate and the ultimate salvage rate for defects of the interventricular septum in infants and still to avoid the high mortality of open-heart surgery in infancy.

SAGALL

Carlier, J., and Lejeune-Ledant, G.: Transmission of Left Atrial Waves to "Pulmonary Capillary" Positions in Dogs with Open Thorax. *Acta cardiologica* 13: 455, 1958.

The effects of thoracotomy on transmission of left atrial pressure to catheters wedged in the pulmonary arteries were studied in 11 dogs. There was a close similarity of atrial and "capillary" pressure curves with regard to the mean pressure and the positive waves; negative waves were sometimes damped in the wedge position. Opening of the chest did not alter the pressure curves on the right side but caused damping of the curves from the left pulmonary artery.

PICK

Gadboys, H. L., Kyle, R. H., and Glover, R. P.: Pulmonic Stenosis with Intact Interventricular Septum. *Surg., Gynec. & Obst.* 108: 175 (Feb.), 1959.

A 7-year experience with a modified Brock-type pulmonic valvulotomy in 46 patients was described. The stenosis appeared to be valvular in 34 patients, infundibular in 6, and combined in 6. The subjective response was good to excellent in 37, fair or poor in 5, undetermined in 3, and 1 patient died of heart failure 8 months postoperatively. The systolic gradient across the pulmonic valve decreased from a preoperative average of 102 mm. Hg to 44 mm. Hg immediately after valvulotomy. Three and one-half years later this gradient (in 21 patients) was 33 mm. Hg. The change in gradient had not always correlated with other evidence of response to operation. While better hemodynamic results have been obtained by open techniques, the overall benefit derived from the simpler closed operation warrants its continued use in isolated valvular pulmonic stenosis in the author's opinion.

ROGERS

Foster, J. H., Berzins, T., and Scott, H. W., Jr.: An Experimental Study of Arterial Replacement in the Presence of Bacterial Infection. *Surg., Gynec. & Obst.* 108: 141 (Feb.), 1959.

Abdominal paraaortic infection was incited in dogs by injecting a saline suspension of feces. Forty-eight hours later, 4 cm. of adjacent aorta was replaced by a frozen homograft or by a woven Nylon prosthesis. When antibiotics were not given or were given only after grafting, nearly all animals died. When antibiotics were begun 24 hours before grafting, 45 per cent of those receiving a prosthesis survived and 16 per cent of those homografted survived. Better results attended the use of more intensive antibiotic therapy. Deaths usually resulted

from peritonitis when a prosthesis was used and from hemorrhage when a homograft was used. Among the survivors, thrombosis of the graft occurred in 14 per cent; and evidence of residual infection was found as late as 18 months postoperatively in 25 per cent of the prosthesis group but in none of the homograft group. It was concluded that in the presence of local infection a synthetic prosthesis was superior to a homograft in terms of survival and also for maintenance of aortic continuity; nevertheless it could act as a focus of chronic infection.

ROGERS

Clotzer, D. J., and Shaw, R. S.: **Massive Bowel Infarction: An Autopsy Study Assessing the Potentialities of Reconstructive Vascular Surgery.** *New England J. Med.* 260: 162 (Jan. 22), 1959.

In a review of autopsy material for a 10-year period at the Massachusetts General Hospital, Boston, undertaken to determine what percentage of patients with bowel infarction could be considered anatomically salvageable by reconstructive vascular surgery, 31 cases were selected for study. Nineteen had fresh occlusions of the superior mesenteric artery or its branches, 3 had old occlusions, and 9 had no demonstrable occlusions. No unequivocal differences in the clinical findings were found in these 3 groups. Of the 19 patients with fresh occlusions at least 15 had arterial obstructions that could have been corrected surgically or were sufficiently distal to allow a small resection of bowel. The importance of a functional element in the cause of bowel infarction and the therapeutic implications are discussed.

SAGALL

Mouquin, M., Dubost, Ch., Maurice, P. and Hatt, P. Y.: **Rupture of Aneurysm of Sinus Valsalvae (with Reference to a Case Operated with Extracorporeal Circulation).** *Arch. mal. coeur.* 51: 935 (Oct.), 1958.

A 37-year-old woman suddenly complained of palpitation and dyspnea, and developed a loud continuous murmur and thrill in the mesocardiac region. Cardiac catheterization showed a left-to-right shunt with pulmonary hypertension. Because of increasing right ventricular failure the patient was operated upon and rupture of the sinus of Valsalva into the right atrium was found. The defect was corrected. A disk oxygenator was used, and the heart arrested by potassium citrate. All clinical symptoms disappeared within 3 months. This is the eighth reported case successfully treated.

LEPESCHKIN

VALVULAR HEART DISEASE

Derra, E., Kaiser, K., and Loogen, F.: **The Clinical Features and Surgical Treatment of Aortic Stenosis.** *German M. Monthly* 3: 137 (May), 1958.

The characteristic clinical, electrocardiographic, and roentgenographic findings of aortic stenosis are described. Four degrees of severity of the condition are differentiated on the basis of the most important clinical symptoms, namely, angina pectoris, syncope, decreased exercise tolerance, and easy fatigability. Group I cases are in the symptom-free stage and show a pressure gradient across the aortic valve of 0 to 40 mm. Hg. Group II patients have moderate symptoms and a pressure gradient of 40 to 80 mm. Hg. Group III and IV patients suffer marked physical limitations and show a pressure gradient across the aortic valve of more than 80 mm. Hg. Group IV patients also present definite evidence of left and even right ventricular failure. The indications for surgery and the various methods of surgical treatment are briefly reviewed and discussed. Data from the author's series of 24 patients operated upon via the transventricular route indicate good results in 4, unsatisfactory results in 2, and 5 deaths occurring shortly after the operation.

SAGALL

VASCULAR DISEASE

Hibbs, R. G., Burch, G. E., and Phillips, J. H.: **The Fine Structure of the Small Blood Vessels of Normal Human Dermis and Subcutis.** *Am. Heart J.* 56: 662 (Nov.), 1958.

The small vessels of the dermis and subcutis of the human fingertip and abdomen obtained by means of punch biopsies were studied with the electron microscope. Two distinctive types of capillaries were found. The ordinary thin-walled capillaries were seen predominantly in the more fatty areas and occasionally among the dense bundles of collagenous fibers of the dermis. These closely resembled the capillaries found in muscle, pancreas, and other organs, and their predominant function apparently was concerned with the exchange of fluid. A second type of vessel never previously reported was found in the vicinity of sweat glands. These vessels were lined by endothelial cells that were thicker than typical endothelium and contained cytoplasmic elements, suggesting that they are actively contractile. It appeared unlikely that these vessels had any important role in the exchange of fluid, and the authors suggested that these vessels by their contractile property played a role in the regulation of the temperature.

SAGALL

Murphy, Q. R., Jr., Gullixson, K. S., Kratochvil, C. H., and Simoes e Silva, J., Jr.: **Circulatory and Renal Adjustments to Acute Femoral Arteriovenous Fistulas.** *Circulation Research* 6: 710 (Nov.), 1958.

The cardiovascular and renal adjustments in blood flow that occurred immediately following the opening of a bilateral femoral arteriovenous fistula were investigated in dogs anesthetized with pentobarbital or morphine and pentobarbital. The volume of blood flow through the arteriovenous fistula averaged 53 per cent of the control cardiac output; however, the cardiac output increased only an average of 27 per cent upon opening the fistula. Since the increment by which the cardiac output increased was only about 51 per cent of the fistula shunt flow, a deficit in body flow occurred. The most prominent renal adjustment associated with opening the fistula was a decrease in renal blood flow and this was more prominent in the animals premedicated with morphine (average decrease was 46 per cent). The authors concluded from this comparison of the per cent reduction in renal blood flow with the per cent reduction in blood flow through the systemic capillary beds that there was no indication that the renal vascular bed shared disproportionately in the circulatory deficit.

PAUL

Gonin, A., Perrin, A., Pellet, M., and Froment, R.: **Dissecting Hematoma of the Aorta.** *Arch. mal. coeur.* 51: 1001 (Nov.), 1958.

Dissecting aortic aneurysm was found in 13 of 1,100 consecutive autopsies; 1 additional case was proved by aortography in a woman with Marfan's syndrome. Nine patients had hypertension, 2 patients had aortic stenosis, and 2 had previous thoracic trauma. In 2 patients rupture occurred in the descending aorta, in 3 at the arch and in 8 near the valves; in 6 of the latter a diastolic murmur of aortic regurgitation was heard. Eight patients showed chest pain, appearing suddenly and usually radiating to the back, neck, or right side. Pericardial friction rub was found in 1, peripheral arterial occlusion in 3, spinal signs in 2 patients. The electrocardiogram was typical of pericarditis in 1 and showed terminal T wave inversion without S-T segment displacement in V_{1-6} in 2 patients; in 1 of these the left coronary artery was compressed by the hematoma, but in the other the coronaries were not involved. Survival of more than 6 months occurred in only 1 of 7 patients with sudden onset of symptoms but in all of 6 patients with gradual onset.

LEPESCHKIN

LEPESCHKIN

Loogen, F., and Wetzels, E.: **Stenosis of the Descending Aorta.** *Ztschr. Kreislaufforsch.* 4: 1061 (Dec.), 1958.

A 30-year-old man had shown for many years marked systolic and diastolic hypertension in the upper but not the lower extremities and sinus bradycardia with only left ventricular hypertrophy in the electrocardiogram. Aortography revealed marked aortic stenosis immediately above the origin of the renal arteries. The patient died after unsuccessful operation and at autopsy this stenosis was shown to have a length of 7 cm. As the renal inulin clearance was normal, the hypertension is considered to result from the stenosis itself rather than from any resulting renal ischemia.

LEPESCHKIN

Daseler, E. H., and Anson, B. J.: **Surgical anatomy of the Subclavian Artery and Its Branches.** *Surg., Gynec. & Obst.* 108: 149 (Feb.), 1959.

The structure and course of the subclavian arteries and their branches were studied in 400 cadavers. The findings were presented in detail along with numerous illustrations of the variations encountered. The surgical relationships of each major vessel were discussed.

ROGERS

Stromblad, B. C. R.: **Effect of Intra-arterially Administered Nicotine on the Blood Flow in the Hand.** *Brit. M. J.* 1: 484 (Feb. 21), 1959.

Nicotine was administered intraarterially via the left brachial artery in 13 experiments on 11 healthy subjects. Blood flow in the corresponding hand (and in a few patients in the right hand) was measured with a venous occlusion plethysmograph. No correlation between the smoking habits of the subjects and the sensitivity to nicotine vasoconstriction was apparent. Nicotine was found to cause vasoconstriction in the hand when injected into the brachial artery. In general, the amount of nicotine assumed to be absorbed during smoking (about 2 mg. of nicotine bitartrate per minute) was sufficient to cause vasoconstriction via a local mechanism. Sympathicolytic and ganglion-blocking agents abolished the effect of nicotine. This appeared consistent with the assumption that nicotine caused a release of sympathomimetic agent from the chromaffin system in the human skin but could also be explained by the existence of a peripheral nervous plexus containing ganglion cells.

KRAUSE

Warren, R., and Villavicencio, J. L.: Iliofemoro-popliteal Arterial Reconstructions for Arteriosclerosis Obliterans: Factors Influencing Late Patency. *New England J. Med.* 260: 255 (Feb. 5), 1959.

A follow-up study of 70 iliofemoropopliteal arterial reconstructions showed a 55 per cent incidence of patency of the reconstructed segments with thrombendarterectomy, 18 per cent for venous autograft, and 9 per cent for arterial homograft. The thrombendarterectomized segments underwent a marked reaction of fibrosis during the first 6 months after surgery but relative long-term patency could be expected with survival beyond this period. With venous autografts it was found that a 6-month survival similarly heralded a good long-term outcome. Closure in the venous autografts presumably resulted from constriction of anastomosis, irregularity of the segment itself, taut adventitial bands, and external hematomas. In both of these groups, therefore, the mechanical factors of suture-line stenosis combined with the factor of fibrotic contracture of wound healing constituted the major threat to late patency. With arterial homografts various lesions such as mural thrombosis, rapid degeneration with calcification, aneurysm, and late degeneration similar to arteriosclerosis were encountered in half of the cases at different times after operation. In this group there was no security against closure with the passage of time. No relationship existed between the incidence of closure of reconstructions and the serum cholesterol level or the incidence of other obliterative arteriosclerotic lesions.

SAGALL

Anderson, R., and Blackwood, W.: The Association of Arteriovenous Angioma and Saccular Aneurysm of the Arteries of the Brain. *J. Path. & Bact.* 77: 101 (Jan.), 1959.

Necropsies were performed on 9 patients with known arteriovenous angiomas; case reports are presented of 5 of these patients who were found to have saccular aneurysms of the cerebral arteries at areas remote from the angiomas. There were 12 aneurysms in all and in 4 patients the aneurysms were multiple. Of the 12 aneurysms, 9 were on feeding arteries and 3 were on nonfeeding arteries; the authors suggest that the aneurysms are not secondary to the angiomas but rather that both conditions are due to a defect of vascular development. Intracranial hemorrhage occurred in 3 patients from an unrecognized saccular aneurysm and none from the clinically recognized arteriovenous angioma.

KARPMAN

Buchholz, R. R.: Arteriovenous Fistula of the Splenic Vessels. *Ann. Surg.* 149: 590 (April), 1959.

Arteriovenous fistulae have been reported following numerous surgical procedures. These seem to occur most commonly when there is mass ligation of arteries and veins particularly when the vessels are ligated with transfixion sutures. The use of needles, wires, pins, and devices for immobilization of bones near the anatomic course of blood vessels has also been a source of such fistulae. This report deals with the occurrence of a fistula between the splenic artery and vein following splenectomy in a 16-year-old boy for congenital hemolytic icterus. The only clinical manifestation was a loud, continuous, machinery type murmur found on routine physical examination. This murmur was located over an area 6 by 6 cm. in the posterior axillary line in the left posterior thorax at the level of the tenth rib. The diagnosis was established 2 years after the splenectomy. The fistula was successfully isolated and excised. Following removal there was no slowing of the pulse. Examinations postoperatively have revealed absence of the bruit. The importance of isolation and individual ligation of blood vessels the size of the splenic artery and vein is emphasized.

LEVINSON

Dominian, J., and Lowe, J.: Spontaneous Thrombosis of External Carotid Artery. *Brit. M. J.* 1: 554 (Feb. 28), 1959.

Since the widespread use of angiography, thrombosis of the common and internal carotid arteries have been often demonstrated. The author reports spontaneous thrombosis of the external carotid artery, confirmed by angiogram in a 65-year-old man. The occlusion in this patient apparently caused severe pain on the right side of the head and numbness of the face. Ordinarily, therapeutic ligation of the external carotid artery for severe epistaxis will cause few or no symptoms. However, in this case the collateral circulation was probably inadequate and hence symptoms occurred with the thrombosis.

KRAUSE

Halpern, A., Selman, D., Shaftel, N., Samuels, S. S., Shaftel, H., and Kuhn, P. H.: The Peripheral Vascular Dynamics of Bowel Function. *Am. J. M. Sc.* 237: 453 (April), 1959.

Alterations in the peripheral circulation occurring in the course of bowel function were studied by estimating peripheral venous pressure, segmental digital arterial blood flow, and peripheral vascular resistance. Data were obtained from groups of normal and constipated indi-

viduals. The straining efforts associated with defecation produced an elevation of the pressure in both antecubital and saphenous veins, with an abrupt return to the base value after the termination of the strain. The use of the bedpan in place of the commode increased the incidence of higher pressure elevations in the antecubital vein, but lowered this incidence in the saphenous vein because of the lack of postural dependence of the venous system of the legs. There was a sharp reduction in segmental blood flow with the onset of straining, which persisted for the period of exertion. With the release of the strain there was transient return of blood flow toward control values followed by a second diminution, after which a vasodilatation occurred before the return to the resting state. During controlled exertions, the venous pressure rose proportional to the magnitude of the straining, and the digital blood flow and pulse volumes showed a pattern of change similar to that of the segmental circulation. In addition there was a marked rise in peripheral segmental and digital vascular resistance. The response was greater in the legs and toes than in the arms and fingers. This resistance was terminated at the conclusion of the strain only to be followed by a sharp increase during the post-strain period. Throughout the study the fluctuations among the constipated group were of a greater magnitude and frequency than those observed among the normal subjects. This reflected the greater straining efforts of this group. When a peristaltic stimulant was administered to the constipated group of patients, there were reductions in the magnitude and duration of the changes. The authors relate these excessive alterations in the peripheral circulatory dynamics during defecation to the occasional dislodgement or fragmentation of a thrombus with subsequent embolism, and suggest that the correction of constipation is of particular importance in the prevention of this catastrophe.

SHEPS

Dodd, H., Wright, H. P.: Vulval Varicose Veins in Pregnancy. *Brit. M. J.* 1: 831 (Mar. 28), 1959.

About 12 per cent of pregnant women develop varicose veins of the vulva. Most women develop these varicosities after the twenty-sixth week of gestation. Multiparous women have a higher incidence than primiparous. Vulval veins become distended from 1 or more of 3 sources of hypertension, namely: the long saphenous vein, the spermatic veins, or the pudendal tributaries of the internal iliac vein. The diagnosis of the various anatomical types of vulval varicosities was discussed. Eradication of these varicosities by surgery, when they caused considerable distress

not relieved by other measures, was frequently beneficial and details are given for the surgical approach to each type.

KRAUSE

Schweizer, W.: The Frequency of Coronary Sclerosis in Aortic Stenosis. *Cardiologia* 33: 5, 1958.

In a search for the causes of the known high mortality of aortic commissurotomy, the author reviewed clinical and autopsy data of 87 patients with isolated calcific aortic stenosis. The investigation revealed a very high incidence of coronary arteriosclerosis in this condition. Normal coronary arteries were present in only about 50 per cent of patients under 50 years of age. Twenty patients had myocardial infarction, attributable in 19 to coronary artery disease. The clinical diagnosis of coronary disease is difficult in the presence of aortic stenosis. It is to be suspected in patients older than 55 years who complain of anginal pain, or give a history suggestive of myocardial infarction, or have an electrocardiogram with an QRS deviation to -60° .

PICK

OTHER SUBJECTS

Thomas, E., and Forbus, W. D.: Irradiation Injury to the Aorta and the Lung. *A.M.A. Arch. Pathol.* 67: 256 (Mar.), 1959.

The paper consists of a case report of a young male on whom, 2½ years prior to his death, a diagnosis of "malignancy, possibly of giant follicular type" was made on a biopsy specimen of a supraclavicular lymph node. He received a course of deep x-ray radiation in the hilar region, estimated to be 1860 r, additional radiation of an unknown quantity 1 year prior to death. Four months prior to his terminal admission he received 1,000 r plus 24 mg. of nitrogen mustard. Initially he presented with dysphagia, dyspnea, nonproductive cough, cyanosis, tachycardia, tachypnea temperature of 104 F., and leukocytosis. He died with increasing dyspnea, cyanosis with wheezing and rhonchi in both lungs. Autopsy revealed irradiation of all traces of the mediastinal lymphoma. Of particular interest were the lungs which showed a remarkably paucity of air and some edema fluid; microscopically, the alveolae and bronchi were filled with a peculiar pink granular material. Alveolar epithelialization was prominent with considerable infiltration by lymphocytes, plasma cells, and foamy macrophages. Cavitation caused by alveolar wall disintegration was also noted. The arch of the aorta was smooth to the beginning

of the transverse segment at which point there was an abrupt change characterized by considerable thickening. The intima bore a striking resemblance to changes usually associated with syphilitic aortitis. This lesion extended from a point 1.5 cm. below the arch of the left subclavian for a distance of 10 cm. The mediastinal mass consisted chiefly of dense collagenous fibrous tissue with calcification and necrosis, while the sternal bone marrow showed a complete absence of all cellular elements. The only apparent complications of the aortic lesion were small splenic and renal infarctions resulting from dislodged thrombi that had formed at the site of the aortic lesion. It was thought by the authors that the pulmonary injury was the predominant lethal factor although the aortic lesion was potentially lethal.

MAXWELL

Duthie, H. L., Irvine, W. T., and Kerr, J. W.: **Cardiovascular Changes in the Post-Gastrectomy Syndrome.** *Brit. J. Surg.* 66: 350 (Jan.), 1959.

This study describes changes in pulse rate, blood pressure, electrocardiogram, packed cell volume, hemoglobin, blood sugar, serum potassium, and plasma volume using I^{131} labeled albumin, one hour before and for 1 hour after oral ingestion of 100 ml. of 50 per cent glucose. Ten such studies were performed in patients with peptic ulcer prior to gastrectomy, 17 studies in patients with Polya gastrectomy, 4 studies in patients before and after conversion from Polya to Billroth I gastrectomy, and 5 studies in patients with gastrojejunostomy. Subjects with intact stomachs showed an increase in pulse rate, little change in blood pressure, to 4 per cent reduction in plasma volume, while the electrocardiogram was essentially unchanged, after administration of glucose. In postoperative patients

pulse rate increased, blood pressure varied inconsistently, and plasma volume decreased 10 to 16 per cent. Changes were similar in all groups, although less marked in the gastrojejunostomy group. Electrocardiographic changes in the postoperative group were more consistent than in the group with intact stomachs. They included T-wave flattening and inversion, and S-T depression in leads II, III and aVf. U-wave formation was also noted. As expected, blood glucose rose in all the groups but no correlation between severity of symptoms and rise in blood sugar or fall in plasma volume was noted. No consistent change was noted in serum potassium.

MAXWELL

REVIEWS IN CARDIOVASCULAR DISEASE

Rushmer, R. F., and Smith, O. A., Jr.: **Cardiac Control.** *Physiol. Rev.* 39: 41 (Jan.), 1959.

Skleton, F. R.: **Adrenal Regeneration and Adrenal-Regeneration Hypertension.** *Physiol. Rev.* 39: 162 (Jan.), 1959.

Miller, J. M.: **Prophylaxis of Rheumatic Fever and Rheumatic Heart Disease.** *New England J. Med.* 260: 220 (Jan. 29), 1959.

Agress, C. M.: **Evaluation of the Transaminase Test.** *Am. J. Cardiol.* 3: 74 (Jan.), 1959.

Brust, A. A.: **Retinopathies Contrasted. Diagnostic and Prognostic Significance of the Optic Fundi in Accelerated Hypertension.** *Am. J. Med.* 26: 81 (Jan.), 1959.

Wood, P.: **Pulmonary Hypertension with Special Reference to the Vasoconstrictive Factor.** *Brit. Heart J.* 20: 557, 1958.

August, J. T., Nelson, D. H., and Thorn, G. W.: **Aldosterone.** *New England J. Med.* 259: 917 (Nov. 6), 1958.

—, —, and —: **Aldosterone II.** *New England J. Med.* 259: 967 (Nov. 13), 1958.

AMERICAN HEART ASSOCIATION, INC.

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Telephone Gramercy 7-9170

STUDY OF HEALTH APPEALS URGED BY AHA BOARD

The Board of Directors of the American Heart Association has resolved to seek the appointment of a group of physicians, scientists and community leaders to study problems arising from the increasing number of health agency fund appeals. The proposed study would create better understanding of the primary health needs of the nation and provide a yardstick for adequate and intelligent support of those health causes which are of greatest concern to the greatest number of people.

The AHA resolution has been endorsed by the Board of Directors of the American Cancer Society. Following is the full text:

"The increasing number of appeals for support made by health agencies has resulted in public confusion. It has diverted attention from the urgent goal of conquering the major chronic diseases which comprise the greatest threat to the health of the nation.

"United Funds and federated campaigns have not provided satisfactory solutions to the problem of multiple health appeals. Furthermore, they are not constituted to provide the leadership and support for the research and other programs essential to the reduction of disability and death caused by the major chronic diseases.

"Since the public interest urgently requires that the utmost support be given to the voluntary health agencies dedicated to the conquest of these major chronic diseases, the Board of Directors of the American Heart Association hereby resolves to seek the appointment of an impartial and qualified group of physicians, scientists and community leaders to undertake a study of the problem of multiple health appeals with the objectives of:

1: Defining the major areas of chronic disease which present the greatest threat to our national health and welfare; 2: Establishing criteria which will guide the public in making voluntary contributions of time, effort and funds to individual health causes."

AHA SCIENTIFIC SESSIONS

The AHA Committee on Scientific Sessions Program has selected 109 original scientific papers from a total of 400 submitted for consideration to be presented at the 32nd Annual Scientific Sessions of the American Heart Association. The Sessions will be held Friday, October 23 through Sunday, October 25 at Convention Hall, Philadelphia.

In addition to panels and symposia at which important clinical problems will be discussed, six clinical sessions will hear a number of investigative papers. One of the clinical sessions will be held jointly with the American College of Cardiology, which is conducting its interim meeting to coincide with the AHA Scientific Sessions. Heart Association members are invited to attend the College's popular "Fireside Conferences."

The Association's Council on Arteriosclerosis will participate in a panel discussion on "Conflicting Concepts of Atherogenesis." Concurrent special scientific sessions and programs will be held under sponsorship of other AHA Councils.

Titles of all papers to be presented and their authors are listed. Information relating to medical films, scientific and industrial exhibits and other features of the program will also be found.

Forms for registering and reserving hotel accommodations are obtainable from the A

Association. Physicians who register in advance will receive a complimentary copy of the program booklet which includes abstracts of the proceedings.

ASSOCIATIONS SUPPLEMENT NATIONAL RESEARCH SUPPORT

AHA affiliates and chapters have contributed nearly \$26,000 through July 7, 1959 to supplement the Association's national research support program for the 1959-60 fiscal year. These funds, which are in addition to amounts regularly assigned by Heart Associations for national research, have permitted support of 6 additional grants-in-aid effective July 1, for which funds would otherwise have been lacking.

In addition to helping reduce a deficit in the national grants-in-aid budget, the new sums aid in underwriting a record total of approximately \$3,300,000 awarded by the National Office for the 1959-60 fiscal period. Associations which have provided funds are as follows:

Genesee County (N.Y.) Heart Chapter, \$800 in partial support of the grants to Julian L. Ambrus, M.D., University of Buffalo School of Medicine, and Harrison F. Wood, M.D., Irvington House; Orange County (N.Y.) Heart Association, \$5,500 in full support of the grant of Burtis B. Breese, M.D., University of Rochester School of Medicine; Napa County (Calif.) Heart Association, \$1,000 and Tulare County (Calif.) Heart Association, \$1,500 in partial support of the grant of Richard J. Havel, M.D., University of California Medical Center.

Also, Livingston County (N.Y.) Heart Chapter, \$1,000 in partial support of the grant of Paul N. Yu, M.D., University of Rochester School of Medicine. As previously reported, the Illinois Heart Association provided \$15,000 in full support of two investigatorships.

Other Heart Associations have pledged an additional \$19,000 through July 7, making total of more than \$44,000 towards the program.

NOVEMBER 1 IS DEADLINE FOR AHA GRANT-IN-AID APPLICATIONS

November 1, 1959 is the deadline for submitting applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1960. All applications must be made on forms available from the AHA and submitted to the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N.Y. Grants are made to non-profit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to five years.

HEART IN INDUSTRY PROCEEDINGS AVAILABLE

Full proceedings of the New York Association Conference on Heart in Industry, in which leading cardiologists, industrial medical directors, labor-management representatives and lawyers participated, are available free of charge to physicians on request from the New York Heart Association, 10 Columbus Circle, New York 19, N.Y. The conference was held January 27, 1959.

SYMPOSIUM ON CARDIOLOGY IN AVIATION MEDICINE

An International Symposium on Cardiology in Aviation Medicine, co-sponsored by the School of Aviation Medicine, Airline Medical Directors Association, and Aero-Space Medical Association, will be held November 12-13, 1959, at Brooks Air Force Base, Texas. Inquiries may be addressed to the Department of Internal Medicine, School of Aviation Medicine, USAF, Brooks Air Force Base, Texas.

MEETINGS CALENDAR

- October 14-17: American College of Chest Physicians, Albuquerque, N. Mexico, Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.
- October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N.Y.
- October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N.Y.**
- November 2-4: Association of American Medical Colleges, Chicago. Ward Darley, 2530 Ridge Avenue, Evanston, Ill.
- November 6-7: Central Society for Clinical Research, Chicago. A. S. Weisberger, 2065 Adelbert Road, Cleveland 6, Ohio.
- November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, N.Y. Hospital, 525 E. 68th Street, New York 21, N.Y.**
- November 9-13: American College of Chest Physicians Annual Course on Diseases of the Chest, New York. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Illinois.
- November 10-12: Conference on Electrical Techniques in Medicine and Biology, Philadelphia. Herman P. Schwan, University of Pennsylvania, Philadelphia, Pa.
- November 12-13: International Symposium on Cardiology in Aviation, Texas. Lawrence E. Lamb, Department of Internal Medicine, School of Aviation Medicine, USAF, Brooks Air Force Base, Texas.
- November 13-14: Annual Symposium on Cinefluorography, Rochester. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N.Y.
- December 7-11: American College of Chest Physicians Annual Course on Diseases of the Chest, Los Angeles. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

1960

- February 3-6: American College of Radiology, New Orleans. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.
- February 18-20: Central Surgical Association, Chicago. Angus D. McLaehlin, Victoria Hospital, London, Ontario, Canada.
- March 19-24: American Academy of General Practice, Philadelphia. Mae F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.
- March 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg. Atlanta 3, Ga.
- March 26-27: American Psychosomatic Society, Montreal. Erie Wittkower, 265 Nassau Road, Roosevelt, N.Y.

ABROAD

1960

- May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N.Y.
- May 6-8: International Congress of Phlebology, Chambéry, France. J. Marmasse, 3 Rue de la République, Orleans, Loiret, France.
- May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.
- August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.
- August 28-September 1: International Congress on Diseases of the Chest, Vienna. A. Sattler, American College of Chest Physicians, Frankgasse 8, Vienna, Austria.
- September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.
- September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

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References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.



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OCTOBER

1959

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PART TWO

Circulation

Official Journal of the AMERICAN HEART ASSOCIATION



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SCIENTIFIC SESSIONS				BUSINESS MEETINGS, LUNCHEONS AND DINNERS	
M O R N I N G	SESSIONS ON CLINICAL CARDIOLOGY	Friday, October 23	Saturday, October 24	Sunday, October 25	Friday, October 23
		Symposium: Regulation of the Cardiovascular System in Health and Disease	Symposia: Recent Developments in Supple- mentary Diagnostic Technics Surgery in Acquired Valvular Disease	Panel: Conflicting Concepts of Atherogenesis Submitted papers of general interest	COUNCIL ON BASIC SCIENCE LUNCHEON AND BUSINESS MEETING Academy Room, Bellevue Stratford Hotel 12:45 P.M.
	SPECIAL AND COUNCIL SESSIONS	COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE COUNCIL ON CIRCULATION	COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH	Instrumental Methods in the Study of the Heart and Circulation Morning Session on Cardiovascular Films	COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE LUNCHEON AND BUSINESS MEETING Clover Room, Bellevue Stratford Hotel 12:45 P.M.
A F T E R N O O N	SESSIONS ON CLINICAL CARDIOLOGY	CONNER MEMORIAL LECTURE: The Performance of the Heart Submitted papers of general interest	Symposium: Congestive Heart Failure BROWN MEMORIAL LECTURE: Circulatory Congestion and Heart Failure Panel: Treatment of Congestive Heart Failure Useful Life After Heart Failure	Symposia: Cardiac Resuscitation Mechanical Methods of Assistance to the Failing Circulation jointly with American College of Cardiology*	COUNCIL ON CLINICAL CARDIOLOGY BUSINESS MEETING Auditorium, Convention Hall 2:30 P.M.
					COUNCIL ON CARDIOVASCULAR SURGERY BUSINESS MEETING Ballroom, Convention Hall 2:30 P.M.
	SPECIAL AND COUNCIL SESSIONS	COUNCIL ON CARDIOVASCULAR SURGERY	COUNCIL ON BASIC SCIENCE COUNCIL ON CARDIOVASCULAR SURGERY jointly with COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE	COUNCIL ON CIRCULATION Round Table Luncheon and Discussion Burgundy Room, Bellevue Stratford Hotel 12:45 P.M.	COUNCIL ON CIRCULATION DINNER AND BUSINESS MEETING Crystal Room, Bellevue Stratford Hotel 6:15 P.M.
E V E		"Fireside Conferences"*			Saturday, October 24 COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH BUSINESS MEETING Ballroom, Convention Hall 12:30 P.M.
					COUNCIL ON COMMUNITY SERVICE AND EDUCATION LUNCHEON Ballroom, Bellevue Stratford Hotel 12:45 P.M.
					Sunday, October 25 ANNUAL DINNER AMERICAN HEART ASSOCIATION Ballroom Bellevue Stratford Hotel 7:30 P.M.

*The American College of Cardiology is holding its Eighth Interim Meeting concurrently at the Benjamin Franklin Hotel.
Monday, October 26—all day Assembly Panel Meetings Bellevue Stratford Hotel
Tuesday, October 27—all day Annual Meeting of Assembly Bellevue Stratford Hotel
Tuesday, October 27—12 noon Assembly Luncheon Bellevue Stratford Hotel

Tuesday, October 27—all day Annual Meeting of Assembly Bellevue Stratford Hotel
Tuesday, October 27—12 noon Assembly Luncheon Bellevue Stratford Hotel

32nd SCIENTIFIC SESSIONS
of the AMERICAN HEART ASSOCIATION

October 23-25, 1959

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Original Communications. Manuscripts for publication, letters and all other editorial communications should be addressed to the Editor-in-Chief, at the above address. Articles are accepted for publication on the condition that they are contributed solely to this journal.

Manuscripts. Duplicate manuscripts, tables and illustrations should be submitted to facilitate selection and processing of papers. Manuscripts should be typewritten on good quality paper, one side of the page only, with double or triple spacing and liberal margins. They should include the authors' degrees and hospital and academic affiliations (for use on the "Contributors" page), and an address for mailing proofs. References to the literature should be compiled at the end of the article in numerical sequence, the style of this journal being observed regarding the full amount of material to be included in each bibliographic entry, the order of material, capitalization and punctuation. If a "Personal Communication" is listed in the bibliography, a letter must be submitted in which the direct quotation is given with the signature of the original author.

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Illustrations and Tables. Position of figures and tables in the text should be marked on manuscript. *Circulation* uses arabic rather than roman numbering. Figures should carry their number and the author's name on the back; figure legends should be compiled in a separate list. To ensure clear reproduction, all copy for zinc cuts, including pen drawings and charts, should be prepared with black india ink,

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Exchanges. Contributions, letters, exchanges, reprints and all other communications relating to the Abstracts Department of *Circulation* should be sent to the Editor-in-Chief at the above address. Writers on subjects which are related in any way to cardiovascular disease are requested to place this address on their permanent mailing list.

Book Reviews. Books and monographs treating specifically of the same subject matter as this Journal will be reviewed as space is available. Send books for review to the Editor-in-Chief, at the above address.

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PROCEEDINGS

of the

32nd SCIENTIFIC SESSIONS

CONVENTION HALL, PHILADELPHIA, PA.
OCTOBER 23-25, 1959

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1958-1959

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The Sessions on Clinical Cardiology* were arranged by the Program Committee of the Council on Clinical Cardiology, jointly with those of the Councils on Basic Science, Cardiovascular Surgery, and Arteriosclerosis.

The Symposia on Cardiac Resuscitation were arranged jointly by the Council on Clinical Cardiology of the American Heart Association and the American College of Cardiology.

*Category 2 Postgraduate Credit for the members of the American Academy of General Practice.

32nd SCIENTIFIC SESSIONS of the AMERICAN HEART ASSOCIATION

Philadelphia, Pennsylvania

October 23-25, 1959

*All Sessions are held at Convention Hall**

TIME LIMIT FOR PRESENTATION OF PAPERS

The Maximum is 10 Minutes for Presentation and 3 Minutes for Discussion

The program of the Annual Scientific Sessions of the American Heart Association is designed to meet the interests and wishes of practicing physicians, specialists in cardiovascular disease, and clinical and basic science investigators. It therefore offers a great variety of presentations which, within the time limitations of three days, are competing for the interest of the participants.

The Committee on Scientific Sessions Program has, after thorough consideration, selected the papers and broad subjects listed in the program. The Committee would welcome any comments regarding the content and format of these sessions, as well as constructive criticisms which may be useful in planning next year's scientific meetings.

FRIDAY MORNING OCTOBER 23, 1959

FIRST SESSION ON CLINICAL CARDIOLOGY

*Arranged by the Council on Clinical Cardiology
and the Council on Basic Science*

Auditorium—9:00 A.M. to 12:30 P.M.

Chairman: Francis L. Chamberlain, San Francisco, Calif.

Co-Chairman: Lewis E. January, Iowa City, Iowa

9:00 Opening Address of the President. Francis L. Chamberlain, San Francisco, Calif.

*The American College of Cardiology will hold the "Fireside Conferences" at the Benjamin Franklin Hotel (see program for Friday evening).

Symposium on Regulation of the Cardiovascular System in Health and Disease

Current Concepts of Cardiovascular Regulation and their Limitations

Significance of Current Concepts in Understanding the Responses of the Cardiovascular System to Stress and Disease

9:10 to 12:30

11:00—INTERMISSION

LYSLE H. PETERSON, Philadelphia, Pa., Moderator

Regulation of Blood Vessel Properties. Lysle H. Peterson, Philadelphia, Pa.

Regulation of Water and Electrolytes. J. Russell Elington, Philadelphia, Pa.

Role of the Nervous System. *Björn Folkow, Göteborg, Sweden*

Regulation of Blood Volume. *Ernest B. Reeve, Denver, Colo.*

Regulation of Cardiac Function. *Robert F. Rushmer, Seattle, Wash.*

Summary. *Robert F. Rushmer, Seattle, Wash.*

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on Rheumatic Fever and Congenital Heart Disease

Exhibition Hall "A"—9:00 A.M. to 12:30 P.M.

Chairman: Currier McEwen, New York, N. Y.

Co-Chairman: John A. Lichty, Denver, Colo.

9:00 **Prevalence of Various Streptococcal Types in Syracuse from 1950 to 1958.** *Harry A. Feldman, Syracuse, N. Y.*

9:15 **Streptococcal Infections in Adolescents and Adults after Prolonged Freedom from Rheumatic Fever.** *Gene H. Stollerman, Eloise E. Johnson, and Burton J. Grossman, Chicago, Ill.*

9:30 **Therapy and Other Factors Influencing the Course of Rheumatic Heart Disease.** *Benedict F. Massell, Shekhar Jhaveri, and Gabor Czoniczer, Boston, Mass.*

9:45 **Effects of Physical Activity in Asymptomatic Patients with Potential or Rheumatic Heart Disease.** *Alvan R. Feinstein, Harry Taube, Ralph Cavaliere, Stanley G. Schultz, and Lawrence Kryle, New York, N. Y.*

10:00 **Rheumatic Fever in Monozygotic and in Dizygotic Twins.** *Angelo Taranta, Seta Torosdag, Irvington, N. Y., Julius D. Metrakos, Wanda Jegier, Montreal, Canada, and Irene Uchida, Toronto, Canada*

10:15 **Efficacy of Penicillin in Eradicating B-Hemolytic Streptococci from Tonsillar Tissue.** *Milton S. Saslaw, James M. Jablon, Sallie A. Jenks, and Claudette C. Branch, Miami, Fla.*

10:30 **Congenital Dextrocardia: Clinical, Roentgenologic, Electrocardiographic, Angiocardiographic, Catheterization, and Autopsy Study of 40 Cases.** *Rene A. Arcilla and Benjamin M. Gasul, Chicago, Ill.*

10:45 **Discussion of papers.**

11:00—INTERMISSION

11:15 **Retrograde Arterial Catheterization of the Left Heart: Experience with 117 Infants and Children.** *Edward C. Lambert and Peter Vlad, Buffalo, N. Y.*

11:30 **Microscopic Study of the Lungs in Tetralogy of Fallot 1 to 12 Years after the Creation of a Systemic-Pulmonary Anastomosis.** *Charlotte Ferencz, Cincinnati, Ohio, and Helen B. Taussig, Baltimore, Md.*

11:45 **Congenital Mitral Insufficiency.** *Norman S. Talner, Aaron M. Stern, and Herbert E. Sloan, Jr., Ann Arbor, Mich.*

12:00 **Clinical and Hemodynamic Studies of 50 Patients with Transposition of the Great Arteries.** *Jacqueline A. Noonan, Alexander S. Nadas, and Abraham M. Rudolph, Boston, Mass.*

12:15 **Familial Muscular Subaortic Stenosis.** *Lawrence B. Brent, Don L. Fisher, Pittsburgh, Pa., and William J. Taylor, Gainesville, Fla.*

Council on Circulation

Ballroom—9:00 A.M. to 12:30 P.M.

Chairman: Herbert Chasis, New York, N. Y.

Co-Chairman: William Goldring, New York, N. Y.

9:00 **Studies of Peripheral Circulation During Sickle Cell Crisis.** *Felice Manfredi, Angelo P. Spoto, Herbert A. Saltzman and Herbert O. Sieker, Durham, N. C.*

9:15 **Clinical Acidosis Due to Lactic Acid.** *William E. Huckabee, Boston, Mass.*

9:30 **Raynaud's Phenomenon as a Guide to Prognosis in Scleroderma.** *Richard G. Farmer, Ray W. Gifford, Jr., and Edgar A. Hines, Jr., Rochester, Minn.*

9:45 **Mechanism of Cardiogenic Shock.** *Santiago V. Guzman, Edward W. Swenson, Robert A. Mitchell and Malcolm D. Jones, San Francisco, Calif.*

10:00 **Circulatory Responses to Hypervolemia and Their Modification by Ganglionic Blockade.** *Robert L. Frye and Eugene Braunwald, Bethesda, Md.*

10:15 **Circulatory Effects of Chronic Hypervolemia in Polycythemia Vera.** *Leonard A. Cobb and Robert J. Kramer, Seattle, Wash.*

10:30 **Effect of Posture and Exercise on Plasma Volume.** *Lloyd T. Iseri, Downey, Calif., Milton G. Crane, Los Angeles, Calif., Etele L. Balatony, and John R. Evans, Downey, Calif.*

10:45 **Prediction of Downward Temperature Drift During Hypothermic Anesthesia.** *Charles A. Hamilton, Bismarck, N. D.*

11:00—INTERMISSION

- 11:15 **Localization of Arterial Obstruction.** *H. Edward Holling, H. Christine Boland, Philadelphia, Pa., and Ellier Russ, Bordentown, N. J.*
- 11:30 **Blood Flow and Oxygen Tension in Vasodilated Skin.** *Raymond Penneys, Philadelphia, Pa.*
- 11:45 **Acute Effects of Cigarette Smoking on the Digital Circulation in Patients with Peripheral Vascular Disease.** *Jack Freund and Clair Ward, Richmond, Va.*
- 12:00 **Pulmonary Capillary Blood Flow Measured by the Plethysmographic Nitrous Oxide Method Compared with the Cardiac Output Measured by the Direct Fick Method.** *Philip Kimbel, Hakan Linderholm, David H. Lewis, Marvin A. Sackner, and Arthur B. DuBois, Philadelphia, Pa.*
- 12:15 **Circulatory Dynamics in Extreme Obesity.** *James K. Alexander and Edward W. Dennis, Houston, Tex.*

FRIDAY AFTERNOON OCTOBER 23, 1959

SECOND SESSION ON CLINICAL CARDIOLOGY

Arranged by the Council on Clinical Cardiology
Auditorium—2:00 to 5:30 P.M.

Chairman: A. Carlton Ernstene, Cleveland, Ohio

Co-Chairman: Hugh H. Hussey, Washington, D.C.

- 2:30 **Expired Air Resuscitation During Cardiac Emergencies.** *David G. Greene and James O. Elam, Buffalo, N. Y.*
- 2:15 **Cause of Dyspnea in Chronic Congestive Heart Failure.** *Peter C. Luchsinger, Thomas J. Ryan, and Kenneth M. Moser, Washington, D. C.*
- 2:30 **Annual Business Meeting of the Council—Including Address of the Council's Chairman.**

3:15—INTERMISSION

- 3:30 **LEWIS A. CONNER
MEMORIAL LECTURE:
The Performance of the Heart**
Louis N. Katz, Chicago, Ill.

- 4:15 **Effect of Human Fibrinolysin (Plasmin) Upon Deep Thrombophlebitis in Man: A Controlled Study.** *Kenneth M. Moser, George C. Hajjar, and Stephen B. Sulavik, Washington, D. C.*

- 4:30 **Relationship of the Electrocardiogram to the Potassium Content of Red Blood Cells.** *Selwyn A. Kanosky, Joseph H. Boutwell, Louis A. Soloff; and with the technical assistance of Doris Rowell, Philadelphia, Pa.*
- 4:45 **Right Ventricular Abnormality: Further Observations on the Employment of Direct Spatial Vectorcardiography.** *Bertram J. Allenstein, Beverly Hills, Calif.*
- 5:00 **Treatment of Heart Block with Chlorethiazide.** *Louis Tobian, Minneapolis, Minn.*
- 5:15 **Prevention of Ischemic Necrosis by Use of Levarterenol-Phentolamine Mixtures in Treatment of Shock.** *Gary Zucker, Robert P. Eisinger, Martin H. Floch, and Mark M. Singer, New York, N. Y.*

SIMULTANEOUS SCIENTIFIC SESSION Council on Cardiovascular Surgery

Ballroom—2:00 to 5:15 P.M.

Chairman: Frank Gerbode, San Francisco, Calif.

Co-Chairman: William W. L. Glenn, New Haven, Conn.

- 2:00 **Dissecting Aneurysms of the Aorta: Critical Analysis of 47 Cases Treated Surgically.** *Michael E. De Bakey, Denton A. Cooley, E. Stanley Crawford, and George C. Morris, Jr., Houston, Tex.*
- 2:15 **Relationship of Hepatic Blood Flow and Oxygen Consumption to Total Systemic Perfusion Rate During Cardiopulmonary Bypass.** *John A. Waldhausen, Carlos R. Lombardo, James A. McFarland, William P. Cornell, and Andrew G. Morrow, Bethesda, Md.*
- 2:30 **Annual Business Meeting of the Council**
- 2:45 **Activation of the Canine Interventricular Septal Surfaces Studied During Cardiopulmonary Bypass.** *Norman S. Amer, Jackson H. Stuckey, Richard R. Cappelletti, and Rodolfo T. Domingo, Brooklyn, N. Y.*
- 3:00 **Peripheral Diffusion as an Indicator of Circulatory Efficiency: Photometric Measurements in 100 Clinical Cases and Their Evaluation as a Guide to Management.** *Ralph Adams, Wolfeboro, N. H., Robert W. Corell, Durham, N. H., and Francis J. C. Dube, Center Ossipee, N. H.*

- 3:15 **Physiologic Extracorporeal Circulation Based on Continuous Monitoring of Blood Gas Tensions.** Bruce C. Paton, Vernon Montgomery, and Henry Swan, Denver, Colo.

3:30—INTERMISSION

- 3:45 **Mitigation of Myocardial Depression Resulting from Elective Cardiac Arrest.** Vallee L. Willman, Theodore Cooper, Panagiotis A. Zafiracopoulos, and C. Rollins Hanlon, St. Louis, Mo.
- 4:00 **Left Ventricular Function Following Elective Cardiac Arrest.** Nina S. Braunwald, John A. Waldhausen, William P. Cornell, Robert D. Bloodwell, and Andrew G. Morrow, Bethesda, Md.
- 4:15 **Surgical Treatment of Aortic Stenosis.** Conrad R. Lam and Rodman E. Taber, Detroit, Mich.
- 4:30 **Surgical Treatment of Valvular Pulmonary Stenosis, Using Extracorporeal Circulation.** F. Gerbode, G. A. Harkins, and J. K. Ross, San Francisco, Calif.
- 4:45 **Experiences with Open Heart Surgery in Pulmonic Stenosis with Right Ventricular Hypertension in Excess of 200 mm. Hg.** George B. Holswade, Mary Allen Engle, Daniel S. Lukas, Frank Glenn, and Henry P. Goldberg, New York, N. Y.
- 5:00 **Intractable Angina Pectoris with Obliterating Coronary Arteriosclerotic Heart Disease in Man Treated by the Operation of Left Atrial-Pulmonary Artery Anastomosis.** Stacey B. Day, Minneapolis, Minn.

FRIDAY EVENING OCTOBER 23, 1959

AMERICAN COLLEGE OF CARDIOLOGY EIGHTH INTERIM MEETING "Fireside Conferences"

Mezzanine of Benjamin Franklin Hotel*

8:30 to 10:30 P.M.

Diagnosis and Treatment of Arrhythmias. Samuel Bellet, Philadelphia, Pa., and David Scherf, New York, N. Y.

*Please note that the "Fireside Conferences" will not be held at Convention Hall and that it will be necessary to register for them upon arrival.

Respirocardiac Failure. David B. Dill, Army Chemical Center, Md., and George R. Meneely, Nashville, Tenn.

Office Diagnosis of Congenital Heart Disease. Benjamin M. Gasul, Chicago, Ill., and Henry A. Zimmerman, Cleveland, Ohio

Use and Abuse of Digitalis. Arthur C. De Graff, New York, N. Y., E. Grey Dimond, Kansas City, Kans., and Samuel A. Levine, Boston, Mass.

Present Status of Clot Lysis. Alvin H. Freiman, New York, N. Y., and Alan J. Johnson, New York, N. Y.

Anticoagulant Treatment of Cerebrovascular Disease. Clark H. Millikan, Rochester, Minn., and Irving S. Wright, New York, N. Y.

Anticoagulant Therapy in Heart and Peripheral Vascular Disease. E. Sterling Nichol, Miami, Fla., and Henry I. Russek, Staten Island, N. Y.

Diet and Atherosclerosis. Edward H. Ahrens, Jr., New York, N. Y., and Louis N. Katz, Chicago, Ill.

Selection of Patients for Artery Replacement. Michael E. De Bakey, Houston, Texas, and Ormand C. Julian, Chicago, Ill.

Use of Enzymes in Diagnosis of Heart Disease. Clarence M. Agress, Los Angeles, Calif., and John S. LaDue, New York, N. Y.

Present-Day Management of Hypertension. B. L. Martz, Indianapolis, Ind., and John H. Moyer, Philadelphia, Pa.

Current Practice in Prophylaxis and Treatment of Acute Rheumatic Fever. Benedict F. Massell, Boston, Mass., Sidney Rothbard, New York, N. Y., and Milton S. Saslaw, Miami, Fla.

Monamine Oxidase Inhibitors. George C. Griffith, Los Angeles, Calif., and Gerhard Zbinden, Nutley, N. J.

Treatment of Refractory Heart Failure. Richard J. Bing, St. Louis, Mo., and Louis Leiter, New York, N. Y.

The Myocarditides. Edgar Hull, New Orleans, La., and William H. Wehrmacher, Chicago, Ill.

Valvular Replacement. Charles P. Bailey, Philadelphia, Pa., and Earle B. Kay, Cleveland, Ohio

SATURDAY MORNING OCTOBER 24, 1959

THIRD SESSION ON CLINICAL CARDIOLOGY

Arranged by the Council on Clinical Cardiology
and the Council on Cardiovascular Surgery

Auditorium—9:00 A.M. to 12:35 P.M.

Chairman: Victor A. McKusick, Baltimore, Md.

Co-Chairman: John W. Kirklin, Rochester, Minn.

Symposium on Recent Developments in Supplementary Diagnostic Technics

9:00 to 11:00

Chairman: Victor A. McKusick, Baltimore, Md.

Invaluable additions to our knowledge of cardiovascular disease have come from special methods of study, but the number and complexity of these technics have increased so rapidly that confusion exists as to their practical application. This symposium will outline the proper use of three of these technics in clinical practice.

- 9:00 **Left Heart Catheterization.** *Eugene Braunwald, Bethesda, Md.*
- 9:30 **Indicator Dilution Technics.** *Earl H. Wood, Rochester, Minn.*
- 10:00 **Cineangiocardiology.** *Frank M. Sones, Jr., Cleveland, Ohio*
- 10:30 **Are History, Physical Examination and Clinical Judgment Outmoded?** *Howard B. Burchell, Rochester, Minn.*

11:00—INTERMISSION

Symposium on Surgery in Acquired Valvular Disease

11:15 to 12:35

Chairman: John W. Kirklin, Rochester, Minn.

- 11:15 **Introduction by the Chairman**
- 11:20 **Surgical Treatment of Acquired Valvular Disease as Viewed by the Internist.** *William Likoff, Philadelphia, Pa.*
- 11:35 **Surgical Treatment of Mitral Stenosis.** *Frank Gerbode, San Francisco, Calif.*
- 11:50 **Surgical Treatment of Mitral Insufficiency.** *Earle B. Kay, Cleveland, Ohio*
- 12:05 **Surgical Treatment of Aortic Stenosis.** *John W. Kirklin, Rochester, Minn.*
- 12:20 **Surgical Treatment of Aortic Insufficiency.** *William H. Muller, Jr., Charlottesville, Va.*

SIMULTANEOUS SCIENTIFIC SESSION

Council for

High Blood Pressure Research

Ballroom—9:00 A.M. to 12:45 P.M.

Chairman: Keith S. Grimson, Durham, N. C.

Co-Chairman: Edward D. Freis, Washington, D.C.

- 9:00 **Antihypertensive Effect of Kidney Transplants.** *Sibley W. Hoobler, Pedro Blaquier, and Arthur Gomez, Ann Arbor, Mich.*
- 9:15 **Clinical Diagnosis of Renal Artery Constriction.** *Edward Meilman, New Hyde Park, N. Y., Abraham Azulay, Hicksville, N. Y., and John M. Butterly, Cedarhurst, N. Y.*
- 9:30 **Rarity of Hypertensive Disease in Paraplegics.** *Joseph H. Magee, Allan M. Unger, and David W. Richardson, Richmond, Va.*
- 9:45 **Demonstration of a Pressor Substance in Renal Vein Blood in Patients with Arterial Hypertension.** *Walter E. Judson and Oscar M. Helmer, Indianapolis, Ind.*
- 10:00 **Preliminary Observations on the Pressor and Hemodynamic Properties of Angiotensin II in Man.** *Frank A. Finnerty, Jr., Gloria D. Massaro, Frederick J. Sigda, and John Tuckman, Washington, D. C.*
- 10:15 **Renal Hypertension Induced by Partial Return of Urine to the Circulation.** *Arthur C. Guyton and William E. Bowles, Jackson, Miss.*
- 10:30 **Interrelationships Between Renin and Electrolytes.** *Herbert G. Langford and Sue Cotten, Jackson, Miss.*
- 10:45 **Further Observations Supporting the Enzyme Deficit Theory of the Cause of Essential Hypertension.** *Milton Mendlowitz, Herbert L. Weinreb, Nosrat Naftchi, and Stanley E. Gitlow, New York, N. Y.*

11:00—INTERMISSION

- 11:15 **Peripheral Venous Distensibility in Essential Hypertension.** *J. Edwin Wood, Augusta, Ga.*
- 11:30 **Clinical and Hemodynamic Effects of a New Antihypertensive Drug.** *David W. Richardson, Eugene M. Wyso, Joseph H. Magee, and Gordon C. Cavell, Richmond, Va.*
- 11:45 **Study of a Large Spectrum of Adrenocortical Hormones in Urines of Normal Subjects and Hypertensive Patients.** *Jacques Genest, Erich Koiv, Wojciech Nowaczynski, and Thomas Sandor, Montreal, Canada*

- 12:00 Failure of Increased Sensitivity to Corticosterone to Account for the Development of Adrenal-Regeneration Hypertension. *Floyd R. Skelton, New Orleans, La.*
- 12:15 Effect of ACTH on the Plasma 17-21-Dehydroxysteroid Levels in Normotensive and Hypertensive Patients. *David Y. Cooper, L. L. Johnson, J. C. Touchstone, and William S. Blakemore, Philadelphia, Pa.*
- 12:30 Business Meeting of the Council.

SATURDAY AFTERNOON OCTOBER 24, 1959

FOURTH SESSION ON CLINICAL CARDIOLOGY

Arranged by the Council on Clinical Cardiology
and the Council on Community Service and Education

Auditorium—2:00 to 5:00 P.M.

Chairman: Eugene A. Stead, Jr., Durham, N.C.

Co-Chairman: Oglesby Paul, Chicago, Ill.

- 2:00 PRESENTATION OF THE ALBERT LASKER
AWARD TO *Robert E. Gross, Boston, Mass.*

Symposium on Congestive Heart Failure

2:15 to 5:30

- 2:15 **GEORGE E. BROWN
MEMORIAL LECTURE:**

Circulatory Congestion and Heart Failure
Ludwig W. Eichna, New York, N. Y.

3:00—INTERMISSION

- 3:15 Panel on Treatment of Congestive Heart Failure.
Eugene A. Stead, Jr., Durham, N. C.:
Moderator
- 3:15 Digitalis—174 Years after Withering:
Mechanism of Action. *Richard J. Bing, St. Louis, Mo.*
Clinical Use. *Calvin F. Kay, Philadelphia, Pa.*
- 3:45 Diuretic Therapy Up-to-Date:
Mechanism of Action. *William B. Schwartz, Boston, Mass.*
Clinical Use. *R. Bruce Logue, Atlanta, Ga.*
- 4:15 Other Measures. *Eugene A. Stead, Jr., Durham, N. C.*

- 4:30 Useful Life After Heart Failure. *Donal R. Sparkman, Seattle, Wash.*
- 5:00 Discussion of the Symposium on Congestive Heart Failure.

SIMULTANEOUS SCIENTIFIC SESSIONS

Council on Basic Science

Ballroom—2:00 to 5:30 P.M.

Chairman: Earl H. Wood, Rochester, Minn.

Co-Chairman: Lysle H. Peterson, Philadelphia, Pa.

- 2:00 Mechanism of the Antiarrhythmic Effects of Sympathomimetic Agents. *Timothy J. Regan, Kenan Binak, Berton L. London, and Harper K. Hellems, Detroit, Mich.*
- 2:15 Direct Studies of Myocardial Contractility in Man. *Robert D. Bloodwell, Leon I. Goldberg, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.*
- 2:30 Relative Inotropic Actions of Some Steroids upon Isolated Cardiac Tissue. *Ralph D. Tanz, Memphis, Tenn.*
- 2:45 Influence of Induced Coronary Insufficiency upon the Left Ventricular Ejection Velocity in the Dog. *G. Octo Barnett, Alexander J. Mallos, Samuel M. Fox, III, and Donald L. Fry, Bethesda, Md.*
- 3:00 Pressure-Volume Curves of the Diastolic Left Ventricle in Man. *Harold T. Dodge, Donald H. Ballew, and Harold Sandler, Seattle, Wash.*
- 3:15 Production of Subendocardial Fibrosis in the Dog. *Albert J. Miller, Ruth Pick, and Louis N. Katz, Chicago, Ill.*

3:30—INTERMISSION

- 3:45 Glycogen, Lactic Acid, and High-Energy Phosphate Levels During Hypothermic Arrest of the Human Heart. *Vincent L. Gott, David M. Long, John A. Johnson, Marilyn M. Bartlett, and C. Walton Lillehei, Minneapolis, Minn.*
- 4:00 Effects of Varying Rates of Sodium Excretion upon Na^{22} Kinetics. *Marvin A. Sackner, Warren D. Davidson, Herschel Sandberg, Leonard J. Fineberg, and Samuel Bellet, Philadelphia, Pa.*
- 4:15 Studies on Salvage of Infarcted Heart Muscle by Fibrinolytic (Plasmin) Therapy. *Irwin Nydick, Paul Rueggsegger, Ramon Abarquez,*

- Claude Bouvier, Robert V. Hutter, Eugene E. Clifton, and John S. LaDue, New York, N. Y.*
- 3:30 **Effect of Insulin Hypoglycemia on Plasma Epinephrine, Serum Nonesterified Fatty Acids (NEFA), and Blood Sugar in Normal Subjects.** *John M. Wallace and William R. Harlan, Durham, N. C.*
- 4:45 **Mechanical Properties of the Pulmonary Artery.** *Dali J. Patel, Donald P. Schilder, Alexander J. Mallos; and with the technical assistance of Alfred G. T. Casper, Bethesda, Md.*
- 5:00 **Influence of Lung Volume on Pulmonary Hemodynamics.** *Daniel H. Simmons, Leonard M. Linde, Joseph H. Miller, and Edward L. Ellman, Los Angeles, Calif.*
- 5:15 **Effects of Hypoxia on Peripheral Venous Tone in Man.** *John W. Eckstein and A. W. Horsley, Iowa City, Iowa*

Council on Cardiovascular Surgery Jointly with Council on Rheumatic Fever and Congenital Heart Disease

Exhibition Hall "A"—2:00 to 5:00 P.M.

Co-Chairmen: James W. DuShane, Rochester, Minn., and Robert E. Gross, Boston, Mass.

- 2:00 **Corrective Surgery vs. Blalock-Taussig Operation Based on 10 Year Follow-Up on Patients with Blalock-Taussig Operation.** *Helen B. Taussig, H. Crawford, S. Z. Palaganio, and S. Zucarodius, Baltimore, Md.*
- 2:15 **Long-Term Clinical and Physiologic Effects of Aortic-Pulmonary Anastomosis in Tetralogy of Fallot.** *Milton H. Paul, Robert A. Miller, and Willis J. Potts, Chicago, Ill.*
- 2:30 **Factors Influencing Results in the Surgical Treatment of Patients with Cardiac Septal Defects.** *Johann L. Ehrenhaft, Montague S. Lawrence, Ernest O. Theilen, June M. Fisher, and William R. Wilson, Iowa City, Iowa*
- 2:45 **Complete Heart Block as a Complication of Repair of Ventricular Septal Defect in Children.** *Ronald M. Lauer, Patrick A. Ongley, James W. DuShane, and John W. Kirklin, Rochester, Minn.*
- 3:00 **Congenital Coronary Arteriovenous Fistula: Clinical, Angiographic, and Physiologic Findings on Five Patients.** *Benjamin M. Gasul, Rene A. Arcilla, Joshua Lynfield, J. Pedro Bicoff, and Lawrence L. Luan, Chicago, Ill.*
- 3:15 **Discussion of Papers.**

3:30—INTERMISSION

- 3:45 **Acyanotic Transposition of the Great Vessels.** *Ali Mehrizi and Helen B. Taussig, Baltimore, Md.*
- 4:00 **Phonocardiography in the Diagnosis of Patent Ductus Arteriosus.** *William M. Rogers, James R. Malm, James S. Harrison, George H. Humphreys, II, and Antonio Demetz, New York, N. Y.*
- 4:15 **Clinical and Physiologic Findings Following Open Surgical Treatment for Aortic Stenosis.** *Harry Goldberg, Joseph F. Uricchio, Janet Dickens, Lamberto G. Bentivoglio, and William Likoff, Philadelphia, Pa.*
- 4:30 **Management of Coarctation of the Aorta During the First Year of Life.** *Franklin J. Harberg, Houston, Texas, and Elton Goldblatt, Johannesburg, South Africa*
- 4:45 **Profound Hypothermia Combined with Extracorporeal Circulation for Open Heart Surgery.** *Will C. Sealy, W. Glenn Young, Jr., Ivan W. Brown, Jr., and Alan M. Lesage, Durham, N. C.*

SUNDAY MORNING OCTOBER 25, 1959

FIFTH SESSION ON CLINICAL CARDIOLOGY

*Arranged by the Council on Clinical Cardiology
and the Council on Arteriosclerosis*

Auditorium—9:00 A.M. to 12:30 P.M.

Chairman: Wright R. Adams, Chicago, Ill.

Co-Chairman: Irvine H. Page, Cleveland, Ohio

Panel on Conflicting Concepts of Atherogenesis

9:00 to 10:45

IRVINE H. PAGE, *Cleveland, Ohio*: Moderator

EDWARD H. AHRENS, JR., *New York, N. Y.*

RUSSELL L. HOLMAN, *New Orleans, La.*

ANCEL KEYS, *Minneapolis, Minn.*

ROBERT E. OLSON, *Pittsburgh, Pa.*

JAMES C. PATERSON, *London, Canada*

FREDRICK J. STARE, *Boston, Mass.*

SIGMUND L. WILENS, *New York, N. Y.*

10:45—INTERMISSION

11:00 **Hourly Variation in Total Serum Cholesterol.**

John E. Peterson, Alan A. Wilcox, Melvin I. Haley, Loma Linda, Calif., and Robert A. Keith, Claremont, Calif.

- 11:15 **Effects of an Inhibitor of Cholesterol Biosynthesis, Triparanol (MER-29), in Subjects with and without Coronary Artery Disease.** William Hollander, Aram V. Chobanian, and Robert W. Wilkins, Boston, Mass.
- 11:30 **Varied Response of Blood Lipid Levels to Altered Food Patterns.** Helen B. Brown and Irvine H. Page, Cleveland, Ohio
- 11:45 **Hypotensive Properties of a New Monoamine Oxidase Inhibitor: DL-Serine-N²-Isopropylhydrazide.** Morton H. Maxwell, Samuel I. Roth, Morton L. Pearce, and Charles R. Kleeman, Los Angeles, Calif.
- 12:00 **Effects of Barbiturates on Coumarin Activity.** Murray Weiner and Peter G. Dayton, New York, N. Y.
- 12:15 **Risk of Interrupting Long-Term Anticoagulant Treatment.** Herbert S. Sise, Jacques Gauthier, and Robert Becker, Boston, Mass.

SIMULTANEOUS SCIENTIFIC SESSIONS

Instrumental Methods in the Study of the Heart and Circulation

Ballroom—9:00 A.M. to 12:30 P.M.

Chairman: Charles E. Kossmann, New York, N. Y.

Co-Chairman: W. Proctor Harvey, Washington, D. C.

- 9:00 **Pathology of the Conduction System in Acquired Heart Disease: II. Complete Right Bundle-Branch Block.** Maurice Lev, Chicago, Ill., Paul N. Unger, Milton E. Lesser, Miami Beach, Fla., and Alfred Pick, Chicago, Ill.
- 9:15 **Preparation of Electrocardiographic Data for Processing and Analysis of Digital Computer.** Hubert V. Pipberger, Edward D. Freis, Leonard Taback, and Henry L. Mason, Washington, D. C.
- 9:30 **Experimental Study on the Origin of T Waves Based on Determinations of the Effective Refractory Period from the Epicardial and Endocardial Aspects of the Ventricle.** Ernest W. Reynolds, Jr., and Condon R. Vander Ark, Ann Arbor, Mich.
- 9:45 **Synthesis of Precordial Leads: Clinical Study of the Dipole Hypothesis of Electrocardiography.** Stanley A. Briller and Robert H. Okada, Philadelphia, Pa.

- 10:00 **Estimation of the Volumes of Blood in the Right Heart, Left Heart, and Lungs in Intact Man by Radioisotope Technics.** William D. Love, Lawrence P. O'Meallie, and George E. Burch, New Orleans, La.
- 10:15 **Measurement of Central Blood Volume by External Monitoring.** Robert H. Eich, William R. Chaffee, and Robert B. Chodos, Syracuse, N. Y.
- 10:30 **Use of Precordial Recording in Studies Involving the Dilution Principles.** Walter H. Pritchard, William J. MacIntyre, Thomas W. Moir, and Frank H. Gott, Cleveland, Ohio
- 10:45 **Clinical Use of Retrograde Left Ventricular Catheterization in Congenital Heart Disease.** Edward W. Green, Robert F. Ziegler, and Doris Kavanagh-Gray, Detroit, Mich.

11:00—INTERMISSION

- 11:15 **Safe and Practical Method of Intravenous Abdominal Aortography, Peripheral Arteriography, and Cerebral Angiography.** Israel Steinberg, Nathaniel Finby, and John A. Evans, New York, N. Y.
- 11:30 **Angiographic Demonstration of Human Inter-coronary Arterial Communications in Vivo.** Richard W. Booth, William Molnar, and Charles V. Meckstroth, Columbus, Ohio
- 11:45 **Use of Gas Chromatography in Detection and Location of Left-to-Right Shunts in Man.** Lloyd H. Ramsey and C. Gordon Sell, Nashville, Tenn.
- 12:00 **Simple Isotope Dilution Technic for Evaluation of Congenital Heart Disease.** Kurt Amplatz, James Marvin, Paul Winchell, Gerardo Gomez, Minneapolis, Minn., and Paul Adams, St. Paul, Minn.
- 12:15 **Detection and Localization of Cardiac Shunts with Injections of Kr⁸³ Solution.** Robert T. L. Long, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

Morning Session on Cardiovascular Films

Exhibition Hall "B"—9:30 A.M. to 12:10 P.M.

J. Edwin Foster, New York, N. Y.: Moderator

- 9:30 **Congenital Anomalies of the Heart. Part I: Normal Embryology.** (Color, Sound, 1959)
Author: George H. Humphreys, II, New York, N. Y.; **Producer:** Sturgis-Grant Productions, New York, N. Y.; **Sponsor:** E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation

Introduction and Discussion: *George H. Humphreys, II, New York, N. Y.*

10:00 Cardiac Output in Man. (Color, Sound, 1959)
Producer and Sponsor: Imperial Chemical Industries, Ltd., London-New York

Introduction and Discussion: *Eugene J. Lippschutz, Buffalo, N. Y.*

10:50 The Mitral Valve: Dynamic Pathology and Surgery. (Color, Sound, 1957)
Authors and Producers: Robert P. Glover, Julio C. Davila, and Robert G. Trout, Philadelphia, Pa; Sponsor: E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation

Introduction and Discussion: *Robert P. Glover, Philadelphia, Pa.*

11:15 The Dynamics of Aortic Valve Disease: Post-mortem Study, Using the Pulse Duplicator. (Color, Sound, 1959)
Authors and Producers: Richard R. Kelley, Fairfield Goodale, Benjamin Castleman, and J. Gordon Scannell, Boston, Mass.

Introduction and Discussion: *Richard R. Kelley, Boston, Mass.*

11:45 Myxomas of the Heart—Diagnosis and Surgical Management: Contrasting Cases in Operative Treatment. (Color, Sound, 1959)
Authors: C. Frederick Kittle and James E. Crockett, Kansas City, Kans.; Producer: Kansas University School of Medicine

Introduction and Discussion: *C. Frederick Kittle, Kansas City, Kans.*

SUNDAY AFTERNOON OCTOBER 25, 1959

SIXTH SESSION ON CLINICAL CARDIOLOGY

Arranged by the Council on Clinical Cardiology and the American College of Cardiology

Auditorium—2:00 to 5:00 P.M.

Chairman: Robert W. Wilkins, Boston, Mass.
Co-Chairman: Osler A. Abbott, Atlanta, Ga.

Symposium on Cardiac Resuscitation

2:00 to 4:00

Osler A. Abbott, Atlanta, Ga., and Ernest Craige, Chapel Hill, N. C.: Moderators

2:00 Presentation of the Problem. *J. Willis Hurst, Atlanta, Ga.*

2:10 Extracardiac Pacemakers and External Defibrillation. *Paul M. Zoll, Boston, Mass.*

2:30 Prevention and Recognition of Cardiac Arrest from the Viewpoint of the Anesthetist. *Paluel J. Flagg, New York, N. Y.*

2:50 Surgical Resuscitation of the Heart. *Claude S. Beck, Cleveland, Ohio*

3:10 Hypothermia as an Adjunct to Cardiac Resuscitation. *Frank Spencer, Baltimore, Md.*

3:30 Summary and Discussion:
Surgical Aspects. Osler A. Abbott, Atlanta Ga.
Medical Aspects. Ernest Craige, Chapel Hill, N. C.

4:00—INTERMISSION

Symposium on Mechanical Methods of Assistance to the Failing Circulation

4:15 to 5:00

Osler A. Abbott, Atlanta, Ga.: Moderator

4:15 Effects of Mechanical Assistance upon Normal and Failing Hearts. *Peter F. Salisbury, Burbank, Calif.*

4:30 Physiologic Principles of Partial Extracorporeal Circulation. *Pierre M. Galletti, Lausanne, Switzerland*

4:45 Clinical Application of Mechanical Assistance to the Failing Heart. *Dwight E. Harken, Boston, Mass.*

SIMULTANEOUS SCIENTIFIC SESSION

Council on Arteriosclerosis

Ballroom—2:00 to 5:00 P.M.

Chairman: James C. Paterson, London, Canada
Co-Chairman: Aaron Kellner, New York, N. Y.

2:00 Fatty Acid Composition of Plasma and Plaque Lipids in Patients Receiving Natural and

- Purified Polyunsaturated Fats.** *Laurance W. Kinsell, George D. Michaels, Priscilla Wheeler, Adolpho Barcellini, and Geoffrey Walker, Oakland, Calif.*
- 2:15 **Adherence to a Prudent Diet and Its Effectiveness in Lowering Serum Cholesterol: Study of 97 Free-Living, Normal-Weight Men, Aged 50 to 59.** *Seymour H. Rinzler, Morton Archer, and Norman Jolliffe, New York, N. Y.*
- 2:30 **Effect of Lipemia on Tissue Oxygen Tension.** *Claude R. Joyner, Orville Horwitz, and Phyllis G. Williams, Philadelphia, Pa.*
- 2:45 **Cine-Coronary Arteriography.** *F. Mason Sones, Jr., Earl K. Shirey, William L. Proudft, and Richard N. Westcott, Cleveland, Ohio*
- 3:30 **Hypocholesterolemic Effects of N-(1-methyl-2,3-di-p-chlorophenylpropyl)-maleamic Acid in Hyperlipemic and Normolipemic Man.** *Bernard A. Sacks, Ethel Danielson, and Robert Sperber, New York, N. Y.*
- 3:15 **Hypercholesterolemia and Nicotinic Acid: A Long-term Study.** *Kenneth G. Berge, Richard W. P. Achor, Norman A. Christensen, Marchelle H. Power, and Nelson W. Barker, Rochester, Minn.*

3:30—INTERMISSION

- 3:45 **Metabolic Studies with Radioactive Heparin in Humans.** *Harold B. Eiber, Isidore Danishefsky, Frank J. Borrelli, and Joseph Litwins, New York, N. Y.*
- 4:00 **Genetic and Environmental Influences on Circulating Lipids: Comparative Study of Two Dissimilar Populations.** *Louis E. Schaefer, David Adlersberg, and Arthur G. Steinberg, New York, N. Y.*
- 4:15 **Excretion of Epinephrine, Norepinephrine and Other Hormones in Men Exhibiting a Behavior Pattern (A) Associated with Coronary Artery Disease.** *Meyer Friedman, Shirley M. St. George, Sanford O. Byers, and Ray H. Rosenman, San Francisco, Calif.*
- 4:30 **Observations on Heparin-Activated and Physiologic Clearing Factor in Health and in Ischemic Heart Disease.** *David F. Brown, Albany, N. Y.*
- 4:45 **Changes in Urinary Catecholamine Excretion Accompanying Carbohydrate and Lipid Responses to Oral Examination.** *Morton D. Bogdonoff, William R. Harlan, E. Harvey Estes, Jr., and Norman Kirshner, Durham, N. C.*

Afternoon Session on Cardiovascular Films

Exhibition Hall "B"—2:00 to 4:15 P.M.

J. Edwin Foster, New York, N. Y.: Moderator

2:00 **Jugular Venous Pulse.** (Color, Sound, 1958)

Author: Paul Wood, London, England
Sponsor: Wellcome Research Laboratories

Introduction and Discussion: *William Dressler, New York, N. Y.*

2:30 **Surgical Considerations in the Treatment of Cerebral Arterial Insufficiency: Study of 110 Patients.** (Color, Sound, 1959)

Authors: E. Stanley Crawford, Michael E. De Bakey, and George C. Morris, Jr., Houston, Tex.

Introduction and Discussion: *Michael E. De Bakey, Houston, Tex.*

3:10 **Cerebral Vascular Diseases: The Challenge of Management.** (Black and White, Sound, 1959)
Produced for the American Heart Association by George C. Stoney Associates, with the assistance of a grant from E. R. Squibb & Sons, New York, N. Y.

Introduction and Discussion: *Leo Dobrin, Forest Hills, N. Y.*

3:50 **Surgical Treatment of Renal Hypertension.** (Color, Sound, 1959)

Authors: George C. Morris, Jr., Michael E. De Bakey, E. Stanley Crawford, and Denton A. Cooley, Houston, Tex.

Introduction and Discussion: *Michael E. De Bakey, Houston, Tex.*

Saturday, October 24, 1959

**COUNCIL ON COMMUNITY
SERVICE AND EDUCATION**

LUNCHEON

Ballroom, Bellevue Stratford Hotel—12:45 to 2:30 P.M.

Address—

The Honorable Arthur S. Flemming, Secretary,
United States Department of Health, Education,
and Welfare, Washington, D. C.

**"The Role of Voluntary Health Associations
in Meeting Future Health Needs"**

SESSION FOR NURSES

Saturday, October 24, 1959

Arranged by the Council on Community Service and Education

Convention Hall—9:00 A.M. to 12:30 P.M.

Registration—Visit Scientific and Industrial Exhibits

Ballroom, Bellevue Stratford Hotel—12:45 to 2:30 P.M.

Council on Community Service and Education Luncheon

(See Program Above)

Clover Room, Bellevue Stratford Hotel—2:30 to 4:00 P.M.

*Panel—"An Experience in the Preparation of the Nurse for the Care of the Patient
with Cardiovascular Disease:" A Report on the University of Minnesota Training
Program*

MARION MURPHY, R.N., Minneapolis, Minn.: Moderator

ABSTRACTS OF PAPERS

LEWIS A. CONNER MEMORIAL LECTURE

The Performance of the Heart

Louis N. Katz, Chicago, Ill.

Not all aspects of this subject will be discussed. Information on the enzymatic and biochemical phases are still too incomplete to warrant presentation. No attempt will be made to depict the sequence of events by which the passing impulse leads to contraction and its subsequent relaxation, nor to describe the machinery of the contracting intracellular material, involving as it does actomyosin and high-energy phosphate.

Instead, attention will be directed to three aspects of the heart:

1. The manner by which the contractile effort of the heart responds to the work load imposed upon it.

2. The factors which determine the oxygen requirements of the heart as its performance is altered.

3. The manner in which the oxygen requirements of the heart are met by coronary flow rate changes and changes in the rate of oxygen extracted from the passing blood.

The importance of muscle tension in establishing the efficacy of the oxygen utilization of the heart will be emphasized. An index of oxygen utilization, the product of arterial blood pressure and heart rate, will be discussed and its value in estimating the oxygen cost of the heart's performance will be stressed.

The role of the external work of the heart on the foregoing variables will be considered and the concept of the so-called mechanical efficiency of the heart will be reduced to its proper importance. The influence of hypoxia, hypercapnia, acidemia, alkalemia, hypocapnia, and of the catecholamines on the manner in which the heart performs, will also be considered.

The purpose of the presentation is to put the known facts concerning the heart's performance in proper perspective—as far as permitted in the time allotted for presentation—so as to enhance our understanding of its behavior under various stresses and in failure.

GEORGE E. BROWN MEMORIAL LECTURE

Circulatory Congestion and Heart Failure

Ludwig W. Eichna, New York, N. Y.

The clinician has long recognized a symptom complex characterized by congestion of venous beds behind either the right heart, the left heart, or both. Since clinical-pathologic correlation indicates that such circulatory congestion most often occurs when the heart is diseased, it has become customary to equate venous circulatory congestion with heart, that is myocardial, failure. There are, however, data which suggest that venous circulatory congestion may occur when the heart, that is the myocardium, is not involved. Such noncardiac circulatory congestion, simulating congestive heart failure, may occur in 3 circumstances: (1) when there is obstruction to the flow of blood in or about the heart, for example, constrictive pericarditis or "pure" obstructing mitral stenosis; (2) when there is excessive retention of water and salt, for example, lower nephron nephrosis with unrestricted fluid intake, excessive administration of salt-retaining steroids, or acute glomerulonephritis; and (3) when there are hyperkinetic circulatory states, for example, hyperthyroidism, anemia and beriberi. These 3 types of venous circulatory congestion differ from typical congestive heart failure associated with diseased hearts in 3 respects: cardiac function appears to be normal or may be supernormal, circulatory function of at least 1 systemic organ, the kidney, appears to be not impaired, and there is little or no improvement in cardiac or renal function in response to specific ionotropic medication (digitalis), either after acute intravenous administration of an optimum dose or following prolonged oral medication. Although patients with congestive heart failure far outnumber patients with noncardiac circulatory congestion, the recognition of the latter group has more than academic significance, for therapy in these patients requires a different approach.

Venous circulatory congestion of itself appears to affect cardiac function in man in a manner which, in general, is consistent with Starling's law of the heart. Lowering ventricular filling pressure by ganglionic blocking agents (Arfonad) or by direct vascular effect (sodium nitrite) leads to an

increase in cardiac output (both agents) and cardiac work (sodium nitrite, but not Arfonad) when the elevated filling pressures of congestive heart failure are lowered. In contrast, cardiac output and cardiac work (both agents) decrease when normal filling pressures are lowered, both in non-cardiac and compensated cardiac subjects. Furthermore, when cardiac subjects in typical low-output congestive heart failure are rendered edema-free by mercurial diuretic therapy alone, the resultant disappearance of venous congestion and fall in venous pressure to normal is often accompanied by an increase in cardiac output (Starling's law holds). This result occurs in approximately one half of the subjects, usually patients in their first or second bout of cardiac decompensation and no further improvement in cardiac function is produced by subsequent digitalis therapy. In the other half of the subjects, usually patients with repeated episodes of congestive failure, relief of symptoms, edema and venous congestion by mercurial diuresis does not result in increased cardiac output. In about half of these patients, cardiac function improves following digitalization; the other half has

such poor cardiac function that there is no increased cardiac output from digitalis therapy.

In all types of patients with venous circulatory congestion, cardiac and noncardiac, the removal of the venous congestion produces relief from the symptoms so characteristically associated with congestive heart failure and this relief is not related to the level of the cardiac output or what happens to it. Follow-up clinical and hemodynamic observations, extending in some instances up to 10 years, in cardiac patients following recovery from first bouts of congestive heart failure, indicate that subjects have lived many years in reasonable comfort in spite of low levels of cardiac output. However, when venous congestion occurs, symptoms always recur. It appears that venous congestion is the "backward failure" hemodynamic abnormality in heart failure and produces the typical symptoms associated with congestive heart failure; low cardiac output is the "forward failure" hemodynamic abnormality and of itself is not symptom-producing but it sharply impairs the supply of blood to peripheral organs and thus is the curtailing determinant of activity.

Abstracts are printed alphabetically according to the senior authors

*Research Fellow, American Heart Association, 1958-1959

†Established Investigator, American Heart Association, 1958-1959

Studies of Arterial Elasticity in the Human

Francois M. Abboud* and John H. Huston, Milwaukee, Wis.

Inhalation of amyl nitrite decreases resistance for a measurable time interval before compensatory effects on heart rate and stroke volume become apparent. The ratio of the resulting change in arterial pulse pressure to the decrease in diastolic pressure forms an "index of arterial elasticity." The reliability of this method depends upon a stable heart rate and an unchanging stroke volume during the critical period of measurement.

A constant stroke volume was demonstrated in all patients by the pulse-contour method ($t = 9.65$, $p < .001$) and in 25 patients by ballistocardiography ($t = 3.0$, $p < 0.01$). A stable heart rate was demonstrated directly.

Arterial elasticity indices were determined in 174 patients from 10 to 90 years old. A linear relationship between chronological ages of 58 normal patients and their arterial elasticity indices was found. Older patients (over 60 years) regularly had arterial elasticity indices greater than 70 per cent.

Twenty-five other patients had diseases frequently associated with premature arteriosclerosis; e.g., arteriosclerosis obliterans, cerebrovascular accidents. Nineteen of them had inelastic arteries (indices > 70 per cent).

In 28 diabetic subjects, frequently premature loss of arterial elasticity correlated well with the severity and duration of the metabolic disorder. In 3 young and relatively mild diabetic subjects, the loss of arterial elasticity was out of proportion to the metabolic disorder.

In 78 patients with arterial hypertension, arterial elasticity correlated well with chronological age and not at all with etiology (labile, neurogenic, essential, renal, accelerated). A few renal and essential hypertensive patients with prema-

ture loss of arterial elasticity had associated diabetes and/or unusually severe or prolonged hypertension.

Acute "Benign, Nonspecific" Pericarditis Associated with the Influenza Virus

Crawford W. Adams, Nashville, Tenn.

Several instances of acute "nonspecific" pericarditis have recently been associated with the viral diseases. Myocarditis, pneumonia, pleurisy, pericardial and pleural effusion, frequently referred to as "complications" of acute "benign" pericarditis, are not "benign" and may be an integral part of a syndrome which we would prefer to call *post-viral myopericarditis*.

The symptoms of acute "nonspecific" pericarditis must often lead to an erroneous diagnosis of myocardial infarction, and it is highly important that the patient not be stigmatized by such an error.

There was an interval of 1 or more weeks between the acute episode of "influenza" and the cardiac manifestations. The clinical features of cardiac enlargement, gallop rhythm, heart block, and elevated SGO-transaminase determinations indicated myocarditis in approximately one-third of these patients.

Fourteen cases of acute "benign, nonspecific" pericarditis are reported which were based on a history of influenza and on significant hemagglutination inhibition and on influenza antibody titer determinations. None of these patients had previously received polyvalent influenza virus vaccine.

The antibody titers demonstrated in 5 cases the type B (Great Lakes) influenza virus; in 4 cases the type A (Japan); in 2 cases the type A (Denver); in 2 cases both type A (Japan) and type B (Great Lakes), and in 1 case both type A (Denver) and type B (Great Lakes) viruses.

SELECTION OF PAPERS: Abstracts of papers and exhibits submitted were evaluated by the Program Committee of the appropriate council or the Subcommittee on Exhibits. The final selections were made by the Committee on Scientific Sessions Program of the American Heart Association on the recommendations of the Council Program Committees. In accordance with committee policy, no senior author was included on the program more than once.

All patients with atypical myocardial infarction, acute "nonspecific" pericarditis, and post-partal heart disease should be carefully evaluated for recent viral diseases as a possible source of the cardiac difficulty.

Clinical Applications of Indirect, Cuffless, Cannulaless Blood Pressure Recording

Ralph H. Adams, Wolfeboro, N.H., Robert W. Corell, Durham, N.H., and Jacqueline A. Lord, Wolfeboro, N.H.

All previously successful methods of recording blood pressures have depended upon: (1) the presence of an intra-arterial cannula; or (2) the creation of jet streams, of which the clinician's cuff and stethoscope are classic examples.

An ideal method would avoid the trauma and hazards of cannulation, while retaining its accuracy. It would equal the convenience of the cuff and stethoscope method, but eliminate its inaccuracy and be safe for constant use over periods of at least many hours. An instrumentation system has been devised, which appears to comply with most of the named theoretical requirements. It is based physiologically upon the long known, and by us reconfirmed, fact of linear relationship between intraluminal pressure and volumetric distention of arteries. It is based physically upon the electrical reaction of capacitance, applied through ionization chamber transducers and by way of sensitive diaphragms, to accurate recording of this relationship in peripheral human arteries. The method is shown, by twin image oscilloscopic tracings, to be of accuracy comparable to intra-arterial cannulation methods, both at steady states and under many variables of physiologic status. Applications in clinical cases have established reliability and safety under conditions of continuous recordings over long periods of time.

Peripheral Diffusion as an Indicator of Circulatory Efficiency: Photometric Measurements in 100 Clinical Cases and Their Evaluation as a Guide to Management

Ralph Adams, Wolfeboro, N.H., Robert W. Corell, Durham, N.H., and Francis J. C. Dube, Center Ossipee, N.H.

The volume of blood passing through the blood vessels beneath the cell of the Millikan-Wood oximeter earpiece at a given instant is directly determinative of the intensity of output signal from the infrared sensitive photoelectric cell. This "IR pulse," separately magnified and recorded through appropriate electronic and mechanical

circuitry, has been analyzed and studied in over 100 clinical cases that have included nearly all variations of physiologic status likely to be encountered in medical and surgical practice. There is a surprisingly accurate reflectivity of minor change in circulatory volume in ear vessels and of such prompt response and repeatability as to make the IR pulse a reliable indicator, and even prognosticator, of changes in stroke volume of blood reaching the vessels of a warm ear.

When suboxygenation occurs, a decrease in IR pulse amplitude appears slightly before changes in arterial saturation can be noted, indicating instantaneous noxious effect of hypoxia on myocardial efficiency. Positive pressure on alveoli, or a rise in expiratory resistance, causes a change in wave form that is detectable within 2 seconds of occurrence.

Carbon dioxide accumulation in venous blood is reflected by reduced IR pulse before a change in respiratory rate appears, and often within 3 seconds of the positive decline in respiratory depth (ventilation).

IR pulse changes (favorable or unfavorable) consistently antecede by more than 30 seconds variations in blood pressure recordings.

An instantaneous and usually notable IR pulse response occurs to manipulative procedures which embarrass cardiac output by pressure on great vessels, by torsion of organs, by heart displacement, by traction on viscera, or by stimulation of autonomic nerves. Chronically or seriously ill, overmedicated or dehydrated cases show marked lability and instability of IR pulse in comparison with those possessing normal reserve.

Significance of Nonatheromatous Intramural Vascular Lesions of the Heart in Diabetes Mellitus

Morris Alex, Sidney Goldenberg, Ram A. Joshi, and Herman T. Blumenthal, St. Louis, Mo.

The present study was designed to obtain information as to the frequency and characteristics of changes in the intramural coronary branches, in both diabetics and nondiabetics. Approximately 100 hearts from patients with myocardial infarction in each of these 2 groups were selected and examined for the frequency of hemodynamic, atheromatous, or inflammatory lesions, similar to those described by Saphir, et al., as well as for vascular changes with characteristics similar to those found in the placentas of diabetic mothers and in extremities with diabetic gangrene, as described by Burstein et al., and Goldenberg et al.

The hemodynamic lesions, characterized by fibroblastic plaque formation, were as common in nondiabetics as in diabetics when the factor of

hypertension was taken into account. As to fat-containing lesions, there was a single case of atheroma in a nondiabetic with primary hyperlipemia, and 1 case of atheromatous embolization in a nondiabetic patient with luetic aortitis.

On analysis of the sections, proliferative lesions of the intramural coronary branches were found in 3/4 (85/116) of the cases with diabetes and in only 1/3 (38/105) of the nondiabetics. On further analysis, based on the sizes of the intramural coronary branches, there was a progressive increase in the frequency of the proliferative lesion among diabetics from the largest to the smallest intramural branches. The inflammatory lesions were found in 1/3 (43/116) of the diabetics and in 1/3 (33/105) of the nondiabetics.

In a previous report, we pointed out that diabetics are more prone to develop subsequent bouts of myocardial infarction following recovery from an initial attack. In this report, we give the evidence for impairment of the potential of an adequate collateral circulation due to lesions in the intramural coronary branches of the caliber of these collaterals.

Circulatory Dynamics in Extreme Obesity

James K. Alexander and Edward W. Dennis, Houston, Tex.

Data relative to cardiac output, vascular pressures and blood volume were secured in 40 obese subjects under conditions of rest and exercise at the time of right heart catheterization. Body weight ranged from 200 to 400 lbs., with an average of 300 or 125 per cent of the predicted ideal weight. With a few exceptions, the subjects were ambulatory and normally active.

Values for cardiac output and circulating blood volume at rest were substantially increased over the predicted values for ideal weight, and were well correlated with weight gain. With weight 100 per cent over ideal, there was a 50 per cent increase in blood volume and cardiac output, the latter associated with increases in oxygen consumption and stroke volume, while A-V oxygen difference remained normal. Mild to moderate systemic arterial hypertension was present in the majority of subjects, but was not well correlated with weight gain. At rest, blood flow per unit weight of tissue was less than normal in the obese subject. However, during exercise, the increase in blood flow per unit increase in oxygen consumption was within normal limits.

Pulmonary hypertension at rest or during exercise was found in the majority of subjects. The accompanying elevation of pulmonary wedge pressure suggested change in left ventricular

filling pressure as the dominant factor in its production. In most cases, hypoxia or intrathoracic pressure change could not be implicated in the genesis of the pulmonary hypertension. Implications of these data in terms of cardiac work and the development of heart failure have been evaluated.

Critical Evaluation of Electrocardiographic Diagnosis of Ventricular Hypertrophy, Based on Autopsy Correlation

Bertram J. Allenstein, Beverly Hills, Calif., and Hiroyoshi Mori, Japan

Five hundred twelve consecutive autopsies at the City of Hope Medical Center served as the basis of this study. Excluded were patients with myocardial infarction, myocardial fibrosis, advanced coronary artery sclerosis, definitive evidence of myocardial bleeding, and those under age 15 years. Sixty-five cases remained for study. Thirty-two patients had anatomically normal hearts, 17 had isolated left ventricular hypertrophy, and 16 had isolated right ventricular hypertrophy. Thickness of the ventricular wall was used as indication of ventricular hypertrophy.

Anatomic findings were compared with electrocardiographic criteria for left ventricular hypertrophy proposed in the American literature. The criteria of Sokolow and Lyon, and of Wilson and co-workers had 88 and 94 per cent accuracy, respectively, in isolated left ventricular hypertrophy. However, they gave a false positive diagnosis of 53 and 78 per cent, respectively, in normal hearts, and 10 and 12 per cent in the presence of isolated right ventricular hypertrophy.

Anatomic findings were compared to electrocardiographic diagnosis of right ventricular hypertrophy as proposed by Sokolow and Lyon, Goldberger, and Myer, Klein, and Stofer. The Sokolow and Lyon criteria gave 75 per cent accuracy with isolated right ventricular hypertrophy. False positives were found, however, in 50 per cent of normal hearts, and 25 per cent of isolated left ventricular hypertrophy.

These observations demonstrate that although we have acceptable accurate criteria for electrocardiographic diagnosis of isolated right or left ventricular hypertrophy, these criteria give an unacceptable high percentage of false positives.

Right Ventricular Abnormality: Further Observations on the Employment of Direct Spatial Vectorcardiography

Bertram J. Allenstein, Beverly Hills, Calif.

Observations on the use of direct spatial vectorcardiography for diagnosis of right ven-

tricular abnormality have been extended to include 250 patients, aged 2 months to 84 years, utilizing the Grishman, Kimura and Frank lead systems. Studies indicated that the electrocardiographic diagnosis of right bundle-branch block is a heterogeneous electrophysiologic grouping. This grouping includes patients who demonstrate: (1) no evidence of block or alteration in the rate of ventricular depolarization, (2) true conduction block, (3) right ventricular hypertrophy without conduction block, (4) right ventricular hypertrophy with conduction block, (5) left ventricular hypertrophy, (6) combined right and left ventricular hypertrophy, and (7) myocardial infarction.

Localized delay in transmission through the right bundle may occur in the presence of a QRS duration of 0.11 seconds or less. Right ventricular hypertrophy may be apparent in direct spatial vectorcardiograms, when classical interpretation of the electrocardiograms, and particularly the right-sided precordial leads are within normal limits. This has been helpful in evaluating early cor pulmonale. The presence of combined right and left ventricular hypertrophy is greatly assisted by direct spatial vectorcardiography in instances where the classical scalar electrocardiogram is inconclusive. In instances where unusual conduction pathways exist, electrocardiographic diagnosis may be inconclusive, whereas direct spatial vectorcardiography frequently provides practical and valuable precision.

Influence of Porphyrin Compounds on Serum Cholesterol in Rabbits

Rudolf Altschul, Saskatoon, Canada

Large doses of nicotinic acid decrease serum cholesterol in man and rabbits and inhibit experimental arteriosclerosis in the latter. Since nicotinic acid is a prosthetic part of the respiratory coenzymes DPN and TPN and its intake increases these coenzymes, trials with injections of respiratory enzymes or their components were made which showed that serum cholesterol in rabbits decreases 5-6 hours after injection of cytochrome-C. Since cytochrome-C possesses a constituent porphyrin moiety, a related compound, hematoporphyrin, was injected into rabbits to test its effect upon serum cholesterol and a highly significant decrease occurred. It was less than that after cytochrome-C (17.18 per cent : 19.66 per cent) but of longer duration. Since the chemical structures of hematoporphyrin and chlorophyll are similar, more recently we injected chlorophyll into rabbits. Twenty-four hours after intramuscular injection of emulsions of chlorophyll (0.5 Gm. in 2 ml. of water) the decrease in serum

cholesterol (-13.8 per cent) was highly significant ($p < 0.001$) although less intense than that observed after injections of cytochrome-C or hematoporphyrin.

Others have used chlorophyll with reportedly good effect in treatment of human arteriosclerosis, but no objective data are available. Blumer fed 10 Gm. chlorophyll daily, together with cholesterol, to each of 8 rabbits and thus prevented arteriosclerosis.

Our experiments indicate that the porphyrin structure, common to cytochrome-C, hematoporphyrin and chlorophyll, influences cholesterol transport and/or metabolism.

Activation of the Canine Interventricular Septal Surfaces Studied During Cardiopulmonary Bypass

Norman S. Amer, Jackson H. Stuckey, Richard R. Cappelletti, and Rodolfo T. Domingo, Brooklyn, N.Y.

Activation of the interventricular septal surfaces of the canine heart has been studied under direct visual control utilizing a technic described previously. By using the pump-oxygenator and cardiopulmonary bypass, it is possible to open the ventricles and to take readings with bipolar surface electrodes at multiple points; reference electrodes are positioned as indicated. Records are monitored on a multibeam oscilloscope and are photographed at speeds of 100-200 mm. sec. Normal activation patterns were determined for each septal surface and after either right or left bundle-branch block. As many as 250 determinations have been taken during 1 experiment without apparent injury to the conduction system.

The earliest depolarization of both the right and left septal surfaces occurs almost simultaneously. On the right, the earliest point activated is anterior and superior to the anterior papillary muscle; on the left, the central portion of the septum is activated first. After right bundle-branch block, conduction is consistently delayed on the right except posteriorly and superiorly with no effect on the left. After left bundle-branch block, the delay in conduction is on the left. Contrary to the findings of some investigators, the left bundle does not activate the region of the septum adjacent to the right anterior papillary muscle.

Simple Isotope Dilution Technic for Evaluation of Congenital Heart Disease

Kurt Amplatz, James Marvin, Paul Winchell, Gerardo Gomez, Minneapolis, Minn., and Paul Adams, St. Paul, Minn.

A simple and sensitive technic has been developed to determine the presence of small shunts.

Forty-five patients and animals with artificially created defects have been examined.

Left-to-Right Shunts. A minute amount of radioactive gas (3-12 μ c. of methyl iodide) is introduced into the left side of the heart as a bolus by 1 single inhalation. Interrupted blood samples are obtained from the right side of the heart through a cardiac catheter, by means of an automatic sampler. In the presence of a left-to-right shunt, radioactive blood is sampled almost immediately after inhalation in relatively high concentrations. The samples are counted in a conventional well counter and the dilution curve obtained is very different from a normal venous return curve which starts several seconds later. If exact quantitation is desired, a simultaneous curve is obtained from one of the peripheral arteries.

Radioactive methyl iodide is very simple to manufacture and is excreted primarily through the kidneys. This property, together with a short biologic half-life and the easily counted gamma emission of iodine, makes it a safe indicator to examiner and patient.

Right-to-Left Shunts. Two to 5 μ c. of radioactive Renografin are injected through a cardiac catheter and interrupted blood samples are obtained from a peripheral artery with the same sampling device. This technic is believed to be far more sensitive than conventional dye-dilution. Peripheral flow can be determined from these curves applying Stewart's principle.

Differentiation between High Pressure IVSD and Patent Ductus Arteriosus. Radioactive Renografin, which has been diluted by saline, is injected into the left brachial artery and forced in retrograde fashion into the aortic arch. At the beginning of the injection, interrupted blood samples are obtained from the pulmonary artery through a cardiac catheter. Immediate appearance of radioactivity in the samples indicates the presence of a patent ductus.

Recordings of the First Derivative of the Human ECG Through the Use of Electronic Analog Computers

Evangelos T. Angelakos, Boston, Mass.

An electronic differentiator was used in conjunction with conventional electrocardiogram amplifiers to obtain tracings of the rate of change of human cardiac potentials from various surface leads. These derivative functions were recorded simultaneously with conventional electrocardiograms from the same leads on a 2 channel recorder. Calibrations were set so that a rate of change of 80 mv. per second corresponded to 10 mm. deflection.

Such records reflect in part the velocity of cardiac excitation and recovery and in part the rate of change in the direction of the maximum potential gradient. This provides information which is not readily available in conventional electrocardiograms and only partially represented in planar or spatial vectorecardiograms.

In normal subjects, the derivative functions of the QRS potentials are smooth curves with 3 main peaks (D_1 , D_2 , D_3). In the conventional leads (with upright QRS), D_1 and D_3 are associated with positive velocities while the major peak D_2 corresponds to a negative rate of change and represents the rapid rate of decreasing potential during the early part of the descending limb of the QRS complex.

Abnormal electrocardiograms obtained from patients had derivative tracings which showed clearly all deviations in the rate of change of the potential during the inscription of the QRS complex thus emphasizing any defects in conduction through the ventricular myocardium. These curves may provide additional criteria in electrocardiogram diagnosis but the patient material studied is too limited to permit a clinical evaluation at the present time.

Congenital Dextrocardia: Clinical, Roentgenologic Electrocardiographic, Angiocardiographic, Catheterization, and Autopsy of Forty Cases

Rene A. Arcilla and Benjamin M. Gasul, Chicago, Ill.

Forty cases of congenital dextrocardia were studied. Physical examination, phonocardiograms, chest x-rays, and electrocardiograms were routinely done. Angiocardiography was done on 29 patients, cardiac catheterization on 8, surgery on 7, and 15 had autopsy. The ages varied from birth to 8 years.

From this study, 4 major types of dextrocardia are described. Type I is mirror-image dextrocardia with the venous chambers anterior to the arterial chambers. Type II is dextroversion complex, complete and incomplete, with the arterial chambers anterior to the venous chambers. Type III is mixed dextrocardia with inversion of either the atria or ventricles. Type IV is congenital extrinsic dextrocardia from anomalies of the lungs, diaphragm, or chest cage. The cardiac displacement is in simple dextroposition or dextroposition with varying degrees of pivotal rotation. Situs inversus was present only in type I. No proven case of isolated mirror-image dextrocardia was encountered in this series or in the literature. The clinically reported cases are probably type II or type III dextrocardia. Our cases of com-

plete dextroversion and mixed dextrocardia had severe cardiac malformations. Tetralogy was the most common and the majority had pulmonary atresia or severe pulmonary stenosis.

The roentgen appearance of types I, II, and III was similar. The oblique views were the reverse of the normal. A low right diaphragm was present in these cases. A right aortic arch was present in 9 of 10 cases in type I. In type IV, an extracardiac disease was always demonstrable. The oblique views were normal in dextroposition alone, but resembled the other types when associated with pivotal rotation. For differential diagnosis the P wave configuration in the standard leads was most helpful. Deep Q and inverted T waves in leads I and AVL were present in 6 of 8 cases with complete dextroversion. The tracings in simple dextroposition were normal. With associated pivotal rotation, deep Q with upright T waves in leads I and AVL appeared. Type III is not diagnosed in the electrocardiogram.

Toward a Rational Dosage of Digitalis in Infants and Children

Natividad Aromin and George W. Thomson, San Antonio, Tex.

Because of the great variability in the dosage of digitalis recommended for use in infants and children, this study was undertaken to attempt to find a maintenance dose that would give the optimum results in the control of congestive failure without toxicity. Consequently, 30 infants and children, varying in age from 2 months to 10 years, were studied, in which an optimum dose of digoxin was established for each individual on an empirical basis. In all cases, there was clear-cut congestive heart failure. Statistical analysis of the data obtained indicate that body weight appears to have the closest correlation with digitalis requirements. A systematic relationship is obtained in dosage vs. body weight for which a regression formula can be described as follows:

$Y = .0023 + 12.5 \times \log \text{body weight in pounds}$, where Y is the maintenance dose, .0023 is ignored, and 12.5 is a constant factor.

The correlation coefficient of this formula is 0.45. The coefficient is the best possible fit (η) of 0.56 and indicates a reasonably good approximation. The standard error of the estimate was found to be 0.05 mg. The maintenance dose was equivalent to the computed optimum dosage, $\pm .05$ mg. for two-thirds of all cases. Fourteen new episodes of congestive heart failure gave an optimum response in 70 per cent of the cases treated. Body surface area did not reveal as close a correlation as with body weight alone.

Endarterectomy for Coronary Artery Disease

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Since our first report of human coronary endarterectomy with survival was published, considerable attention and effort has been devoted to the surgical removal of atheromatous lesions of these arteries.

Several basic observations make direct surgical attack upon these lesions rational and possible. First, the arterial segments involved by the process are upon the heart surface and are surgically accessible. Second, the disease most frequently systematically involves the arteries in a pathologic pattern, usually in segmental fashion. Third, the distribution of the process is characteristically in the epicardial portion of these arteries where they are of such size as to be successfully operable.

The profession's lack of acceptance of indirect surgical procedures for chronic coronary arterial disease has provided additional impetus to efforts toward the development of a direct surgical approach as a solution to the nation's number 1 medical problem.

During the past 3 years, the technic of coronary arteriography has been improved to the point that it now is possible to demonstrate the localization and extent of intra-arterial disease prior to operation. It has been necessary to develop a new technic and new surgical instruments for the performance of these operations. Experimental work has shown consistent myocardial fiber changes subsequent to 40 minutes of occlusion of a coronary artery. The combination of extracorporeal pumping with autogenous lung oxygenation and hypothermia provide maximum cardiac protection during the period of actual removal of the intra-arterial atheromatous lesion.

Quantitative Immunologic Studies on Serum β -Lipoprotein Fractions in Recent Myocardial Infarction

Saul P. Baker and A. S. Markowitz, Chicago, Ill.

In 1953, production of an antiserum to an ultracentrifugally-derived serum β -lipoprotein spectrum, S_f 2-30, from dogs on a thiouracil-cholesterol atherogenic dietary regimen and its use in precipitin tests was reported. Recently, using pooled sera freshly obtained from patients with recent myocardial infarction, it has been possible to separate 3 β -lipoprotein fractions, S_f 10-100 (fraction I), S_f 5-15 (fraction II), and S_f 3-9 (fraction III) in bulk utilizing a dextran sulfate complex and the ultracentrifuge. Antiserum to each fraction was then produced in rabbits. Specificity of each antiserum was estab-

lished by differential absorption with the other 2 lipoprotein fractions. Quantitative determination of β -lipoprotein protein nitrogen for each fraction in whole sera tested was accomplished by micro-Kjeldahl analysis of precipitates.

To date, 44 patients with recent myocardial infarction have been evaluated. Fraction I demonstrated a mean of 1.44 mg. per cent protein nitrogen (range 0.93 to 1.70); in fraction II, the mean was 0.80 mg. per cent protein nitrogen (range 0.62 to 1.05); and in fraction III, the mean was 4.72 mg. per cent protein nitrogen (range 3.96 to 5.10). In 6 normal subjects, the mean for fraction I was 0.62 mg. per cent (range 0.49 to 0.72); for fraction II 0.42 mg. per cent (range 0.38 to 0.49); and for fraction III 2.36 mg. per cent (range 2.01 to 2.70).

These results suggest that quantitative immunologic studies of the specific protein moieties of fractions of ultracentrifugally-derived serum β -lipoproteins may be of value in evaluating coronary atherosclerosis in man.

Influence of Induced Coronary Insufficiency upon the Left Ventricular Ejection Velocity in the Dog

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A catheter tip method of approximating instantaneous blood velocity was used to evaluate the changes in proximal aortic ejection velocity in the dog following acute induced changes in coronary blood flow. Ventricular and aortic pressures were measured by catheter manometer systems, "myocardial contractile force" by the strain gauge arch method of Walton and Brodie, and "fiber length" by the recording calipers of Mallos. The coronary blood flow was altered both by acute arterial ligation and diffuse coronary embolization with microspheres.

The changes in aortic velocity were compared with alterations in aortic pressure, left ventricular end-diastolic pressure, rate of the ventricular pressure rise, as well as changes in "fiber length" and "contractile force" in the area of ischemic myocardium. Reproducible, rapidly occurring changes in the ejection velocity curve followed acute coronary ligation. These changes included a decrease in maximum acceleration, peak velocity, average ejection velocity, duration of ejection, and diminished myocardial contractility in the ischemic area. These effects were reversible if the occlusion was maintained for only a few minutes.

Preliminary work on diffuse coronary embolization in the closed chest dog demonstrated similar changes in aortic velocity contour.

This method of velocity approximation appears

to offer a sensitive means for the evaluation of myocardial function following induced alteration of coronary flow in the experimental animal. These studies form a useful foundation for the evaluation of the effect of coronary disease on myocardial function in human subjects to which the method is being applied.

Hemodynamic Determinants of Auscultatory Phenomena in Pulmonic Stenosis with Open and Closed Septa

Alceo Barrios and Calhoun Witham, Augusta, Ga.

Phonocardiograms, pressures and flows were studied by standard techniques. Valve areas were estimated at surgery and by hydraulic formulas with satisfactory agreement; auscultatory features were correlated with this data.

The duration of splitting of the second sound fundamentally varies:

$$\frac{\text{Right ventricular stroke volume}}{\text{Valve diameter}}$$

and can be modified by appropriate changes of these parameters. Casual right ventricular pressures were not closely correlated with splitting because of flow variation, even in isolated stenosis. This is more obvious when either septa is open. Most tetralogies have less splitting than expected because of low valve flows and some trilogies have more because of high flows. The loudness of P_2 is more related to pulmonary pressure (and valve area) and relatively independent of valve flow changes. Increasing the pulmonary pressure by shunt operations always intensifies P_2 .

The configuration of the stenotic murmur is determined by the following: lateness of maximum intensity

$$\propto \frac{\sqrt[2]{\text{Stroke vol. right ventricle}}}{\text{Diameter}}$$

Even moderate surgical increase in diameter shifts the peak earlier, but rather large flow changes are necessary to change murmur profile (valsava, amyl nitrite, etc.). The frequency of early "infundibular type" murmurs in the tetralogy is related to low valve flow rather than site of obstruction.

Although valvular incompetence is probably common, its murmur is rarely heard in right stenosis because of small retrograde flow. Postoperative frequency is high. Ejection sounds also appear postoperatively or with milder obstruction, since rapid distention of the artery is necessary.

Combined Use of Cineangiofluorography and Cardiac Catheterization in Diagnosis of Anomalous Pulmonary Venous Drainage

Fouad A. Bashour, Carleton B. Chapman, and Hugh Wilson, Dallas, Tex.

The localization of insertions of anomalous pulmonary veins has been found more accurate when cardiac catheterization is combined with cineangiofluorography than when the former technic alone is used.

Cinefluorographs were taken at $7\frac{1}{2}$ or 15 frames per second, following the injection of hypaque through a no. 9 cardiac catheter.

Cardiac catheterization localized the site of the shunt in 5 studied cases but, unlike cineangiofluorography, failed to elicit the origin and number of pulmonary veins participating in the left-to-right shunt.

In 1 case of pulmonic stenosis with arterialization of right atrium and superior vena cava, the catheter entered no unusual channels. Cineangiofluorography showed a large pulmonary venous trunk extending upward from the left lung toward the superior vena cava. This was proved at surgery. In another case, a right-sided anomalous venous trunk was found at catheterization, apparently entering the right atrium. Cineangiofluorography and subsequent operation showed that it entered the inferior vena cava. Similarly, in 2 additional cases, anomalously inserted right pulmonary veins were observed entering the superior vena cava. In the final case, the cardiac landmarks were confused by the presence of dextrocardia. This technic established the location of right ventricle, pulmonary artery and confirmed the presence of an anomalous pulmonary venous trunk entering the venous atrium.

Abdominal Angina: A Clinical Syndrome

Fouad A. Bashour, Dallas, Tex.

Three males and 1 female (31 to 72 years of age) were admitted with severe abdominal pains, variable in character, localized in the midabdomen and radiating widely. The pain appeared in the postprandial period and lasted in 1 case up to 3 hours. The pain existed 5 months to 2 years prior to demise. The appetite was unaltered, but patients feared food, lived on liquids, and lost weight.

The youngest patient had an acute myocardial infarction 2 months prior to the appearance of abdominal pain; at the onset, the pain was intermittent. A cholecystectomy performed 3 months later did not relieve the pain. Five months after surgery he developed a left hemiplegia. A trial

on nitroglycerin before meals resulted in complete relief of the abdominal pain.

In case 4, the patient had syphilitic involvement of the aorta with aortic insufficiency, saccular aneurysm of the ascending aorta. The pain was excruciating, occurring 3-4 times a day, worsened by meals. At surgery, there was extreme spasm of the smaller intestinal arterioles. A biopsy of the stomach wall showed partially occluded arterioles. Following intra-arterial copavarine, arterial spasm abated, and the biopsy site bled profusely.

The relationship of the pain to meals is essential in the diagnosis of this syndrome. Nitroglycerin was helpful in alleviating the pain in 1 case diagnosed antemortem. Recognition of this syndrome is extremely important since generalized intestinal infarction following exploratory surgery is the principal cause of death.

Pulmonary Vascular Resistance Following Closure of Atrial Septal Defect in Patients with Pulmonary Hypertension

Walter Beck, H. J. C. Swan, Howard B. Burchell, and John W. Kirklin, Rochester, Minn.

Eleven patients with pulmonary artery systolic pressures in excess of 60 mm. Hg were studied before and 3 to 34 months after surgical closure of atrial septal defects.

Preoperatively, pulmonary artery mean pressures (P_{pa}) averaged 40 mm. Hg (range 35-60), and pulmonary vascular resistance (R_{pv}), 510 dynes sec. cm^{-5} (range 190-760). Postoperatively, significant reductions in P_{pa} and Q_{pv} averaging 21 mm. Hg and 3 L. per minute, respectively, occurred. Wedge pressure exceeded preoperative right atrial pressure by an average of 5 mm. Hg (range 2 to 12). R_{pv} increased in 1 patient from 760 to 850 dynes. In 4 with preoperative R_{pv} 's of over 600 dynes, it fell by 85, 70, 64, and 36 per cent; in the remaining 6 with preoperative values, ranging from 190 to 440 the average fall was 26 per cent (range 11 to 63).

No correlation existed between the magnitude of drop in R_{pv} while breathing 100 per cent oxygen preoperatively and the postoperative change. Of 6 patients exercised postoperatively, 3 showed no change in R_{pv} ; in the remainder it increased by 51, 47 and 23 per cent.

The postoperative drop in R_{pv} in some cases to near normal levels at rest suggests an increase in caliber of resistance vessels, the most likely cause being reduction in vasomotor tone. The response of the pulmonary vasculature to exercise, however, remains abnormal. Whether resolution of organic change occurs is uncertain.

Follow-Up Studies upon Infants with Coarctation of the Aorta and Patent Ductus Arteriosus

M. Remsen Behrer, Frederick D. Peterson, and David Goldring, St. Louis, Mo.

Infants born with coarctation of the aorta and an intra- or extracardiac shunt frequently develop congestive failure early in life which is resistant to intensive medical treatment. Surgical correction of the defects is, therefore, indicated as a life-saving procedure.

Ten infants with the above malformations were operated upon. Eight survived, of whom 7 were in congestive heart failure and 1 had a history of failure. Seven of the 8 had marked systolic hypertension and the blood pressure gradients between the upper and lower extremities varied between 40-130 mm. Hg.

Seven of the patients were 4 months and under at the time of operation and 1 was 18 months. Seven patients had a patent ductus arteriosus demonstrated at operation, in addition to the coarctation.

The survivors have been followed from 1-4 years postoperatively and have been re-evaluated. The following information has been gathered. 1. No hypertension has been demonstrated in any patient. 2. Four patients have normal blood pressure gradients between the upper and lower extremities and 4 patients have only a 10-20 mm. Hg gradient. 3. Four patients show definite evidence of an intracardiac defect (1 patient was shown to have an interventricular septal defect). In the remaining 4 patients, there is no clinical evidence of additional cardiac defects.

We feel that this experience reaffirms our conviction that early surgical intervention in infants with coarctation and additional cardiac defects is feasible and life saving. There are no indications that the coarctation was re-established in these patients during this period of follow-up.

Use of an Internal Cardiac Pacemaker in Treatment of Slow Heart Rates and Cardiac Arrest

Samuel Bellet, Otto F. Muller, Philadelphia, Pa., Antonio C. deLeon, Washington, D.C., Lawrence D. Sher, William Lemmon, and David Kilpatrick, Philadelphia, Pa.*

Several types of pacemakers, both internal and external, can be utilized in increasing slow heart rates or restoring cardiac beating during cardiac arrest. We wish to discuss our experience in the use of a transistor pacemaker (Atronic Pacer) for cardiac stimulation in both the closed and open chest. In the open chest, the stimulating

electrode may be introduced through the fourth intercostal space with a specially designed needle. Evidence of contact with the myocardium is indicated by oscillations of a galvanometer needle. This pacemaker presents a number of interesting features: (1) it is small and easily portable (weight, approximately 2 pounds), and thus can be carried by the human subjects; (2) it is a constant current source, with automatic voltage adjustment; (3) it is effective with small currents (2 to 10 mA.), thus eliminating the need for high voltages; (4) contractions of intercostal or chest muscles are noted; (5) following resuscitation of the exposed heart, further trauma is avoided by attachment of this pacer; (6) a galvanometer denotes the actual activation wave of the heart muscle, giving information as to heart rate and rhythm; and (7) battery life during continuous usage is about 4 months.

The instrument was tested in 36 dogs with normal sinus rhythm, complete A-V heart block, and cardiac arrest. Effective heart beats with adequate blood pressure response were maintained over long periods of time. This pacemaker has since been used successfully in human subjects with Stokes-Adams seizures and episodes of cardiac arrest.

Sensitivity of the Ventricular Pacemaker in Complete A-V Heart Block to Acidosis and Hyperkalemia: Clinical and Experimental Study

Samuel Bellet, Philadelphia, Pa., Antonio C. deLeon, Washington, D.C., and Otto F. Muller, Philadelphia, Pa.*

Four patients with complete A-V heart block were studied to determine the role of electrolyte changes preceding multiple Stokes-Adams seizures. It was found that the presence of acidosis (pH and CO₂ changes) and/or the occurrence of hyperkalemia were factors in precipitating many of these attacks. Repeated observations were made over a period of weeks (4 months in 1 case) and revealed that when the acidosis and hyperkalemia appeared, the Stokes-Adams seizures recurred; correction of the acidosis and hyperkalemia resulted in a remission of the seizures. It is also of interest that in these patients, Isuprel was not particularly efficacious in the usual dosage, while molar sodium lactate alone or molar sodium lactate in conjunction with Isuprel had a more salutary effect in the treatment of the acute attack and in preventing subsequent seizures.

Experimental observations relative to the effect of acidosis in depressing the ventricular pacemaker in experimental complete A-V heart block

have been made in this laboratory. The effect of hyperkalemia was studied in 8 dogs with complete A-V heart block. The ventricular pacemaker was shown to be extremely sensitive to increases in potassium, as illustrated by a decrease in idio-ventricular rate from 70 to 15 beats per minute with K levels of 8 mEq./L. Similar degrees of hyperkalemia produced in dogs with normal sinus rhythm had only a slight effect on the heart rate.

These observations suggest that the ventricular pacemaker is extremely sensitive to the effects of acidosis and/or hyperkalemia. The findings are of interest in the pathogenesis as well as in the therapy of Stokes-Adams seizures occurring in complete A-V heart block.

Apexcardiogram in the Diagnosis of Mitral Disease

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The inaudible, low frequency (below 30 c.p.s.) vibrations of the precordium have been recorded as the apexcardiogram (ACG of the left ventricle). The particular movement of the chest wall in diastole can be delineated as the filling phase of the left ventricle.

The ACG was recorded with phonocardiogram as reference tracing. Analysis of the ACG was made in each case with special attention given to the rapid filling wave (RFW). Three angles were determined; the rapid filling angle (R) was the angle the RFW made with the baseline. The slow filling angle (S) was the angle formed by the bottom of the ascending limb of RFW and the ascending limb of systolic wave. The total angle (T) was measured from the bottom of RFW to the top of the systolic wave.

In cases of predominant mitral stenosis, the RFW disappeared or became very small. In this group, the R angle could not be determined and the S angle varied from 10 to 30° (average 23°). There was a good correlation between the S angle and size of the mitral valve, as determined at surgery. The ACG was repeated in 15 patients after mitral valvulotomy and significant increase in the S angle and appearance of RFW occurred in most of the cases. The S angle in the post-operative group ranged from 31 to 71° (average 58°).

In cases of predominant MR, a RFW was present in all of them and the R angle ranged from 42 to 81° (average 62°).

The analysis of the RFW of the ACG by this method appears to give a very reliable index of the relative size of the mitral valve.

Electrocardiogram and Hemodynamics in 500 Proven Cases of Congenital Heart Disease

Lamberto G. Bentivoglio, Sheldon Bender, Vladir Maranhao, Leonard Dreifuss, Daniel Downing, and Harry Goldberg, Philadelphia, Pa.

An electrocardiographic study of 100 cases each of atrial septal defect (ASD), ventricular septal defect (VSD), ventricular septal defect plus pulmonary stenosis (VSD plus PS), pulmonary stenosis (PS), and patent ductus arteriosus (PDA) was performed and a correlation between electrocardiogram and right ventricular systolic pressure was attempted. The predominant QRS patterns in V_1 were: ASD, rSR¹ (70 per cent); VSD, RS (40 per cent); VSD plus PS, R (s) (51 per cent); PS, (q) R (s) (45 per cent); PDA, rS (95 per cent). Right ventricular hypertrophy was present in 94 per cent of ASD, 65 per cent of VSD, 93 per cent of VSD plus PS, 72 per cent of PS and 5 per cent of PDA. The pattern of right bundle-branch block was seen in the majority of cases with ASD but was not confined to this group.

The correlation between degree of right ventricular hypertrophy and right ventricular hypertrophy on the electrocardiogram proved satisfactory only in severe PS. Left ventricular dominance was a frequent finding in PDA (48 per cent) and was not uncommon in VSD with low right ventricular pressure. "Diastolic overload" of the left ventricle was rarely seen in either PDA or VSD. The correlation between hemodynamic data and combined ventricular hypertrophy on the electrocardiogram proved unsatisfactory. The sharing of identical QRS patterns in V_1 and V_6 by different congenital cardiac lesions mediates against a specific anatomic diagnosis on electrocardiographic basis alone.

Congenital Aortic Valve Disease

Lamberto G. Bentivoglio, Javier Sagarminaga, Joseph Uricchio, and Harry Goldberg, Philadelphia, Pa.

Eighteen patients make up this series, 14 males and 4 females, their ages ranging from 7 to 32 years. Seventeen presented the following types of aortic stenosis proved by open heart surgery: supra-aortic, 1; valvular, 10 (bicuspid, 7 and tricuspid, 3); subvalvular, 6. One had surgically proved, uncomplicated, bicuspid aortic valve.

The aortic murmur was always discovered before the age of 5. There was no history of sub-acute bacterial endocarditis. Symptoms, when present, included exertional dyspnea, fatigue, vertigo, syncope, and angina. All patients had thrills and grade III or IV aortic systolic mur-

murs. Seven (1 bicuspid) presented early blowing diastolic murmurs. The second sound was usually normal except in subvalvular stenosis where it was absent or reduced.

Electrocardiograms and roentgenograms ranged from normal (uncomplicated bicuspid valve) to left ventricular hypertrophy and aortic dilatation. All but the patient with uncomplicated bicuspid aortic valve showed aortic pressure gradients on left heart catheterization and evidence of aortic stenosis at surgery. Uncomplicated bicuspid aortic valves mimic clinically the stenotic types and only normal electrocardiograms, roentgenograms and hemodynamics afford their differentiation. Stenotic bicuspid aortic valves form a major share of congenital aortic obstructions, are not abnormally susceptible to subacute bacterial endocarditis, and are usually competent. Absence or reduced intensity of the second aortic sound appears to be a constant finding in subaortic stenosis. Congenital aortic valve disease includes a gamut of malformations ranging from uncomplicated bicuspid valves to severe types of obstruction. Occasionally valvular and subvalvular stenosis coexist.

Left Ventriculography and Dye-Dilution Curves in Mitral Valve Disease

Bernard Bercu, Eric Carlsson, and Milton Kardesch, St. Louis, Mo.

The separation of patients with mitral stenosis from those with mitral insufficiency has continued to plague the cardiologist in spite of improved diagnostic methods. In an attempt to provide objective evidence of the degree of mitral regurgitation in these patients, angiography with injection of a radio-opaque dye into the left ventricle was selected for study.

Right heart catheterization was performed to determine pulmonary vascular pressures. Cardio-green dye was injected via the cardiac catheter into the main pulmonary artery and a dye-dilution curve recorded from blood simultaneously withdrawn from the radial artery. A second catheter was passed via the right radial artery and aorta into the left ventricle. Angiography was then performed with injection of the contrast medium into the left ventricle. The degree of opacification of the left atrium was graded by comparing the maximum increase in density of the left atrium with that of the left ventricle after injection of the radio-opaque material.

Fifteen patients have been studied in this manner. Of these, 6 had a significant degree of mitral insufficiency. In 1 of these the dye-dilution

curve suggested mitral stenosis. Nine patients had essentially pure mitral stenosis. The dye-dilution curve correlated well in these cases. Left ventricular angiography also permitted estimation of the size of the left ventricle, aortic valves, and aorta.

It is concluded that left ventriculography is a safe, objective method for the study of mitral valve disease.

Metabolic Cardiopathy: Acquired Heart Disease Associated with Abnormal Connective Tissue Metabolism

Gerald S. Berenson, New Orleans, La.

A concept of cardiovascular disease arising from a disturbance of metabolism of connective tissue is suggested particularly by 2 genetically transmitted clinical syndromes: Hurler (gargoylism) and Marfan. Recent major advances in identification of chemical units of connective tissue and considerations of these units as dynamically active, biochemical substances support this concept.

A study of 19 cases, including 3 autopsies, of the Hurler syndrome and observations by others indicate that approximately three fourths of these patients develop heart disease, evidenced by valvular insufficiency, myocardial hypertrophy, endocardial thickening and nodulation of mitral cusps, frequent deaths from congestive heart failure, and interestingly, extensive coronary atherosclerosis. Furthermore, these patients accumulate excessive amounts of acid mucopolysaccharides (MPS) in various organs and excrete qualitatively and quantitatively abnormal quantities of MPS in urine.

Cardiovascular disease is recognized as part of the Marfan syndrome. Evidence is accumulating to indicate that the disease is a progressive disorder due to biochemical error(s). Studies of 5 individuals with the Marfan syndrome and 3 *forme fruste*, indicate urinary excretion of quantitatively abnormal amounts of MPS.

The various MPS have characteristic distributions in many tissues, including cardiovascular structures, and presumably play important physiologic roles. The nature of the defect in the syndromes presented and the manner in which metabolic disturbance produces heart disease—a metabolic cardiopathy—remain to be understood. Studies of these syndromes, although infrequent in over-all scope of cardiovascular disease, may yield useful information concerning diseases with less obvious metabolic disturbances of connective tissue.

Hypercholesteremia and Nicotinic Acid: Long-Term Study

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Nicotinic acid (niacin) was administered orally to 63 hypercholesteremic persons, in doses varying from 1.5 to 6.0 Gm. per day for periods of up to 3½ years. Type or content of dietary fat was not altered. A placebo was administered for 3 months during the first year of study.

The mean value for plasma cholesterol (mg. per 100 ml.) for 47 persons completing at least 1 year of study, the percentage decrease from the pretreatment value, and the daily dosage of niacin were, respectively: pretreatment 322; 0-3 months, 266 (-17 per cent), 3.0 Gm.; 4-6 months, 249 (-23 per cent), 3.8 Gm.; 7-9 months, 249 (-23 per cent), 3.9 Gm.; and placebo interval 301 (-7 per cent). Nine persons maintained a mean decrease of cholesterol from a pretreatment level of 311 to 211 (-32 per cent) during their third year on treatment (3.9 Gm.); none has become refractory during continued use of niacin.

Cutaneous flushing and pruritus noted initially in all persons subsided promptly in most instances. Anorexia and nausea occurred occasionally and caused 3 persons to discontinue treatment. A battery of 5 tests of liver function gave normal results in 29 cases. In 10 instances, 1 or more tests gave transiently abnormal results, but in 6, these reverted to normal without interrupting treatment. Two persons have had persistently abnormal tests with continued treatment. None exhibited clinical signs of hepatic disease. Mild but reversible elevations of fasting blood sugar or abnormal glucose-tolerance tests developed during treatment in nearly two-thirds of persons so studied.

Treatment of hypercholesteremia with niacin has several practical advantages including effectiveness, simplicity and economy of administration, and lack of need for dietary restrictions. However, such treatment must be proved safe over long periods before it can be regarded as other than investigational.

Nephelometric β -Lipoprotein Determination in Patients with Arteriosclerosis

Peter Bernfeld, Cambridge, Mass.

A new method for the determination of serum β -lipoprotein had been introduced earlier. The procedure was found to be specific for β -lipoprotein; it is based on the precipitation of this protein from whole serum by amylopectin sulfate, and on the quantitation of the precipitate by nephelo-

metric measurements. The new method may supplement other procedures such as ultracentrifugation and paper electrophoresis because of its simplicity, rapidity, and accuracy, and because it requires only minute amounts of serum (0.1 ml.). The nephelometric method is, therefore, a valuable tool for large scale clinical β -lipoprotein surveys.

In the present study, serum β -lipoprotein of 1,324 individuals was determined by the nephelometric method. The mean β -lipoprotein concentration in 753 patients with various arteriosclerotic manifestations was 780 mg. per 100 ml. of serum, with a standard deviation of 197. A group of 294 subjects of over 40 years of age with no known disease exhibited a mean β -lipoprotein concentration of 666 mg. per 100 ml. (S.D. = 164). Statistical evaluation of the data yielded a *t* value of 8.76 for the difference between the 2 groups, thus proving a high degree of significance. Mean β -lipoprotein concentrations were also increased in patients with kidney and liver diseases, diabetes, hypercholesterolemia, and in obese persons, while patients with malignancies and with various other diseases showed no significant changes. These data demonstrate the usefulness of nephelometric β -lipoprotein determinations in patients with arteriosclerosis.

Effect of Intracardiac Acetylcholine Infusion upon Right and Left Heart Dynamics in Rheumatic Heart Disease

William H. Bernstein, Philip Samet, Miami Beach, Fla., and Robert S. Litwak, Miami, Fla.

The potentialities of the pulmonary vascular bed for vasodilation continue to be a subject for intensive investigation. Current interest has centered in acetylcholine. Measurements of heart rate, cardiac output, and pulmonary and systemic artery pressures were made at rest before and during infusion of acetylcholine, at rates varying from 0.5 to 2.25 mg./min. into the right atrium and ventricle. In 13 subjects, these data were also obtained during exercise. Determination of mitral diastolic and aortic systolic gradients were carried out in 5 patients before and during acetylcholine infusion. The rate of this infusion was adjusted to prevent a systemic hypotensive effect. In 12 studies, the resting mean pulmonary artery pressure was less than 20 mm. Hg. In this group, the control average pulmonary artery pressure and cardiac index were 23/9, 14 and 2.49 L./min./M.², respectively. During acetylcholine infusion, the corresponding data were 21/8, 13 and 2.45. In 20 studies, the resting pulmonary artery mean pressure ranged between 20-50 mm. Hg. In this group, the control average

pulmonary artery pressure and cardiac index were 46/22,31 and 2.31. During acetylcholine infusion, the corresponding data were 43/21,29 and 2.32 L./min./M.² In 2 subjects (mean pulmonary artery pressure more than 50 mm. Hg), the respective data were 113/45,67 and 2.01, and 108/42,66 and 1.97. The changes during exercise were similar, except for a larger increment in cardiac output during acetylcholine infusion. In 5 subjects, the mean left atrial-left ventricular mean diastolic gradient was 14 mm. Hg before and during acetylcholine infusion. The small change in pulmonary artery pressure during acetylcholine infusion in these subjects is in contrast to the large decrement noted in 1 subject with primary pulmonary hypertension.

Importance of Multiple Precordial Leads

David Biber, Union, N. J., Edwin L. Rothfeld, and Frank Feldman, Newark, N. J.

Electrocardiograms were surveyed daily in the electrocardiograph laboratory and those which showed changes in the precordial leads, but not in the limb leads, were selected. Vectorecardiograms of these patients were then taken using the cube system. Since the cube system does not use precordial electrode placement, it was not difficult to find 6 patients in whom the horizontal plane vectorecardiograms failed to yield important information given by the conventional precordial electrocardiograms.

Next, vectorecardiographic lead systems using precordial electrodes were analyzed by diagrams of image space and lead vectors. It was shown that the use of resistance networks alters the image space of the patient so that some points on the precordium have no representation in image space and important information is lost.

In electrocardiograms with changes localized over a small part of the precordium, the dipole generator must shift during the cardiac cycle during inscription of the complexes. An abrupt shift may take place between the inscription of QRS and T. This means that the lead vectors and image space are not constant but may vary during the cardiac cycle. Thus the value of quantitative lead vector determinations made on models with a fixed position dipole is limited.

All of these facts emphasize the importance of multiple precordial leads.

Histologic Changes in Experimental Segmental Coronary Thrombosis and Myocardial Infarction

Emil Blair, Baltimore, Md.

A gradually occluding segmental coronary thrombosis and myocardial infarction with a sub-

stantial survival rate was produced by introducing a spiral aluminum-magnesium alloy wire into a coronary artery (distal to the septal branch) of pentobarbitalized dogs. This alloy induces blood clotting. The spiral holds the vessel lumen open by stretching the wall, thus allowing continued, although diminishing, blood flow as the gradually occlusive process takes place, with resultant myocardial infarction. Coronary thrombosis developed in 100 per cent of the animals and myocardial infarction in 95 per cent. Sixty per cent survived the infarction. The thrombosis and infarction, as determined by serial electrocardiography (ECG) and serum glutamic oxalacetic transaminase (GOT) levels, occurred anywhere from 3-12 days with the majority in 6-10 days. The surviving animals were sacrificed at periodic intervals up to 3 months for histologic study. GOT levels rose and fell secondary to surgery and a second elevation at the time the infarction developed. ECG demonstrated classic S-T segment changes during the acute infarction and healing.

Recanalization of the thrombosis was seen within 60 days. The infarction showed the classic picture of fragmentation with loss of architecture accompanied by hemorrhage and inflammatory exudation. This was followed by development of profuse vascular activity, fibroblastic and collagen activity and finally healing by scar. The line of demarcation between the infarct and normal myocardium was singularly distinct in all phases. The preparation resembles the mechanically produced aspects of clinical myocardial infarction and offers a satisfactory medium for physiologic and surgical exploration.

Effect of Rapid Whole Blood Transfusion and of Noradrenalin on Posthypothermic Circulatory Insufficiency

Emil Blair, Baltimore, Md.

Chloralosed dogs cooled (surface immersion technique) and maintained at 30 C. for 1 hour and then rewarmed (surface immersion technique) exhibit acute circulatory failure, manifested by reduced cardiac output and increased A-V oxygen difference. The insufficiency might be due either to myocardial or to peripheral vasomotor reflex failure. In an attempt to elucidate the mechanism involved, the following studies were done: 1. Rapid whole blood transfusion of estimated 1/3 blood volume directly into the right atrium. 2. Intravenous infusion of noradrenalin (NA), 0.09-1.0 µg./Kg./min. Adequate controls were obtained for each group. An incipiently or early failing heart, suddenly overloaded, would be expected

to go into frank failure. This did not occur in group 1. The infusion of NA in group 2 resulted in a return of cardiac output and of A-V oxygen difference to normal.

The mechanism of the circulatory insufficiency seen on rewarming may occur as follows: During hypothermia, in response to reduced metabolic demands, perfusion is reduced by way of shunting blood from the "effective" circulation into the "stagnant" circulation (or reservoirs). Upon rewarming, as the metabolic rate increases, blood flow should increase by mobilization of blood from the reservoirs and reintroduction into the "effective" circulation. Failure of restoration could give the picture of circulatory insufficiency and is suggested by restitution with NA. It has been demonstrated by von Euler that NA is effective in mobilizing blood from its reservoirs. It appears then that at least 1 mechanism responsible for the posthypothermic circulatory insufficiency is a failing peripheral vasomotor, possibly a venomotor, reflex.

Pepper, Mustard and Ginger in Hypertension and Coronary Disease

Jackson Blair, Cleveland, Ohio

Proneness to hypertension in nationality groups of Slovak, Hungarian and Italian descent, and of American Negroes, was noted in an active industrial and private practice. The common link appeared to be the great consumption of pepper and condiments in their diet.

In 1948, the author reported 50 cases and presented the theory that excessive eating of the condiments, especially pepper, mustard and ginger, is a common cause of hypertension; it may be produced experimentally by excessive feeding of these condiments and the damage may be irreversible. The author believes these theories have been demonstrated to be true. In a pilot experiment, rats maintained on diets, which included pepper, mustard and ginger, developed hypertension.

In 1957, Roth and Blair reported further experiments in which statistically significant hypertension, persisting for months after these condiments were discontinued, was produced in rats.

Since that time, the author has pinpointed the chemical in mustard, allyl-isothiocyanate, thought to be responsible, and in feeding experiments, Roth and the author have produced hypertension in all experimental rats on breeders diet plus allyl-isothiocyanate. This work appears to open an entirely new approach to the etiology of atherosclerosis and coronary disease.

Selection of Patients for the Surgical Treatment of Hypertension

William S. Blakemore, Peter J. Jannetta, Gordon K. Danielson, and John J. Murphy, Philadelphia, Pa.

Among the lesions which may cause hypertension and which can be corrected by surgical treatment are: pheochromocytoma; occlusion of the aorta, renal arteries or their branches; and unilateral kidney disease. Essential hypertension with progressive vascular damage, despite vigorous medical therapy, may be effectively treated by established surgical procedures in a high percentage of patients.

Several new diagnostic techniques are useful in the selection of patients for surgical treatment. Urine from more than 300 hypertensive patients has been analyzed by a fluorometric and a recently modified bioassay techniques for measuring catecholamines. Values of greater than 150 μg . per day may indicate the presence of a pheochromocytoma. In 9 patients with tumors, the catecholamine excretion was greater than 250 μg . per day. Diurnal variation and other causes of false positive or negative results by either test have been investigated. Unusual signs and symptoms were present for more than 20 years in 2 patients. Roentgenographic technique, using perineal CO_2 injection or venous and selective arterial renal angiography have been developed to locate and demonstrate the lesions. Two specially designed scintillation counters are utilized for the estimation of renal blood flow and renal function using I^{131} -labeled contrast media. The safety of these methods permits their use for screening a greater number of selected patients with essential hypertension.

Direct Studies of Myocardial Contractility in Man

Robert D. Bloodwell, Leon I. Goldberg, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

Direct-vision intra-cardiac operations, performed with the aid of total cardiopulmonary bypass, provide the opportunity for the measurement of the direct effects of drugs and surgical procedures on myocardial contractility in man. The Walton-Brodie strain gage arch was sutured to the right ventricle in 29 patients undergoing such operations and continuous recordings of the isometric tension of this portion of the ventricle were made. Prior to perfusion, the comparative effects of sympathomimetic amines were studied in 15 patients. Both norepinephrine and epinephrine, in equivalent doses, produced pronounced increases in cardiac contractile force. Vasoxyl, in equi-

pressor doses, had little effect on the myocardium. Aramine and Wyamine caused a sustained increase in contractility. Ten patients without evidences of congestive heart failure were acutely digitalized with acetylthioflavine during cardiopulmonary bypass. A marked increase in myocardial contractile force was noted after 5 minutes, was maximal in 15 minutes, and persisted. These studies indicate that digitalis preparations significantly increase myocardial contractility in the nonfailing human heart.

The strain gage arch was also employed in 9 patients to study the alterations in contractile force occurring during extracorporeal circulation with anoxic cardiac arrest or selective coronary perfusion. Following these interventions, myocardial contractile force was shown to be little impaired. These studies have established that increases in myocardial contractility occur in man after the exhibition of sympathomimetic amines and digitalis preparations. The technic has also been found a safe and practical one for assessing the inotropic effects of other drugs, anesthetic agents, and methods employed during thoracic surgical operations.

Effect of Adrenocortical Steroid in the Radiologic Differentiation of an Enlarged Mediastinal Image

Sidney Blumenthal, John Caffey, and Sylvia P. Griffiths, New York, N.Y.

The normal thymic enlargement seen in patients of the pediatric age group has often made radiologic interpretation of cardiomegaly, or of abnormal supracardiac vascular structures, difficult. The administration of prednisone, because of its capacity to cause temporary involution of the thymus gland, has proved useful in visualization of the mediastinal cardiovascular structures.

Observations have been made on patients in whom the response to prednisone has clarified the presence or absence of cardiac pathology. Four illustrative cases have been investigated. There were 2 patients with suspected congenital heart disease, due to total anomalous pulmonary venous drainage: in 1 of them, the massive mediastinal shadow, visible on consecutive chest x-rays, disappeared after elective steroid therapy, whereas the persistence of the supracardiac shadow in the other patient was subsequently confirmed by angiocardigram as being caused by anomalous pulmonary venous channels. In the third case, unsuspected dextroversion of the heart became manifest radiologically after the patient had received prednisone for treatment of possible myocarditis. In another patient, following cessation of steroid therapy for acute rheumatic fever,

serial chest x-rays illustrated apparent progressive cardiac enlargement; prompt regression of the silhouette occurred after a test trial of prednisone.

Diminution of extracardiac masses, due to thymic tissue, has been achieved by the administration of prednisone in a daily dose of approximately 10 mg. for 5 days. Our experience has demonstrated the value of elective steroid therapy in the evaluation of enlarged cardiomyic shadows.

Changes in Urinary Catecholamine Excretion Accompanying Carbohydrate and Lipid Responses to Oral Examination

Morton D. Bogdonoff, William R. Harlan, E. Harvey Estes, Jr., and Norman Kirshner, Durham, N.C.

The role of the autonomic nervous system in mediating alterations in cardiovascular and metabolic responses to a psychologically meaningful stimulus has been studied in normal subjects during a real-life stressful situation. Sixteen senior medical students were observed before, during, and after a 15 minute oral examination, the outcome of which could alter the time of graduation.

Serum glucose rose in all subjects (mean = +10 mg. per cent), serum nonesterified fatty acid (NEFA) levels rose in all subjects (mean = +450 μ Eq./L.), heart rate increases ranged from 10-90 beats per minute (1 student demonstrated a consistent rate of 140-170 during the examination). In 9 of the students, urinary catecholamines were measured by the bio-assay technic. Urinary adrenalin levels increased in all (mean = 0.6 μ g./hr.; a one third to twenty fold rise). Urinary noradrenalin increased in 6 subjects (mean = 1.6 μ g./hr.; a one half to nine fold increase) and decreased in 3 subjects (mean = 0.9 μ g./hr.; a 10 to 50 per cent change). The magnitude of the increases in glucose and serum NEFA levels demonstrated a direct correlation; there was no such direct correlation between the quantitative change in adrenalin or noradrenalin levels and the magnitude of the serum glucose or NEFA change.

These studies provide direct evidence that there is a simultaneous change in indicators of carbohydrate and lipid metabolism during an acutely stressful real-life situation, accompanied by significant changes in catecholamine excretion.

Angiographic Demonstration of Human Intercoronary Arterial Communications in Vivo

Richard W. Booth, William Molnar, and Charles V. Meckstroth, Columbus, Ohio

The angiographic demonstration of intercoronary arterial anastomoses following infarction is not well documented in the literature. We encountered 2 cases with such communications in 42 coronary angiograms utilizing the transcarotid approach for injection. A nylon catheter (3 mm. O.D. and 2.5 mm. i.d.) is introduced into the aortic sinus without obstructing cerebral blood flow for more than 40 to 50 seconds. We injected 35 to 45 ml. 90 per cent Hypaque (diatrizoic acid) in a period of 3-4 cardiac contractions and films were taken with biplane technic at 6 per second. Details of the angiograms obtained were demonstrated by a normal arteriogram and one showing occlusion of the main right coronary artery without coronary backflow. Intercoronary arterial anastomoses were first observed in a patient with aortic stenosis and angina without electrocardiographic evidence of infarction. Angiograms showed retrograde filling of the obstructed left circumflex branch via an abnormal branch arising from the right coronary artery. The next case, with a myocardial infarct 10 years earlier, showed occlusion of the left main coronary artery with retrograde filling of all of its branches from the right. This was confirmed by surgery and proven 6 months later at postmortem. There have been no fatalities or major complications in connection with 42 injections. Serial electrocardiograms during and following the procedure have shown only minor and transitory ST-T wave changes.

Preparative Ultracentrifugation and Fractional Lipoprotein Concentrations: Description of Six Distinctive Serum Types

Edwin Boyle,[†] Jonolyn Wilson, and Robert V. Moore, Charleston, S.C.

A preparative ultracentrifuge technic, using sodium sulfate to adjust solvent density, has been perfected. This method permits a direct rapid cholesterol analysis of serum fractions without dialysis, whereas other salts interfere markedly with cholesterol determinations. This technic permits 3 significant serum fractions to be measured: (1) a high density (α) lipoprotein fraction, density > 1.063 ; (2) low density (β_1) lipoproteins, density < 1.063 and > 1.006 ; and (3) the very low density lipoproteins (β_2), density < 1.006 .

Six distinctive lipoprotein patterns have been distinguished, using total serum cholesterol values, serum lipoprotein fraction cholesterol values, total lipid values, and K-agar β -lipoprotein precipitation values. Of these 6 types, type 1 is considered "normal" and the other 5 are specific deviations. Sera from 2,306 persons were studied. Of these, 1,017 were judged "abnormal" by having above or below "normal" values. Ultracentrifuge data

for type 2 (785 cases) show an elevated β_1 -cholesterol concentration. Type 3 (29 cases) shows low α and β_1 with very high β_2 -cholesterol values. Type 4 (17 cases) shows a low α with marked elevated β_1 - and β_2 -cholesterol content. Type 5 (117 cases) is characterized by a low α , elevated β_1 - and a moderately elevated but stable β_2 -cholesterol value. Type 6 (69 cases) has a low α , normal β_1 and a moderately elevated β_2 -cholesterol content.

It is suggested that these lipoprotein patterns are due to different lipid metabolic errors or combinations of them. Response to diet and drugs usually follows predictable alterations in cholesterol content of these fractions.

Coagulation Defects in Patients on Long-Term Anticoagulant Therapy

Paul W. Boyles and E. Sterling Nichol, Miami Beach, Fla.

The major contraindication to anticoagulant therapy is hemorrhage. There are 2 different types of bleeding seen in patients on long-term anticoagulant therapy: One type is associated with a markedly prolonged prothrombin time. The other type of bleeding is associated with a prothrombin time in the commonly accepted therapeutic range; namely, 25 to 40 seconds. Bleeding in the former instances is easily explained on the basis of the marked delay in the clotting mechanisms. Bleeding in the latter instance occurs frequently in patients on long-term anticoagulants and is not clearly understood.

Evaluation of the relative importance of the various coagulation factors in bleeding associated with a prothrombin time in the therapeutic range forms the basis of the present investigations. Determinations of the various coagulation factors have been maintained on long-term anticoagulant therapy from 1 to 10 years. The data have been analyzed with reference to various anticoagulants and the clinical history of bleeding. These studies have shown that the coagulation defects in this group of patients is remarkably similar and has little relationship to the clinical history of bleeding. In addition to the known effects on depression of prothrombin and SPCA, all of these patients have a serum defect which is shown clearly by the thromboplastin generation test. This serum defect has been shown to be due to varying degrees of deficiency of PTC, Hageman factor and Stuart factor. Coagulation studies have been performed on a group of 35 patients bleeding from anticoagulant therapy with a prothrombin time in the therapeutic range. Serial studies indicate variation in these defects in 2 patients with hemorrhage from anticoagulant therapy. In

addition, studies have been made of various prothrombin methods, various tissue thromboplastin preparations and serum electrophoresis in patients on long-term anticoagulant therapy.

Left Ventricular Function Following Elective Cardiac Arrest

Nina S. Braunwald, John A. Waldhausen, William P. Cornell, Robert D. Bloodwell, and Andrew G. Morrow, Bethesda, Md.

Acute heart failure is occasionally observed following a period of elective cardiac arrest induced in the course of an intracardiac operation employing cardiopulmonary bypass. This complication was encountered in patients without severe pulmonary hypertension or other lesions predisposing to failure, and suggested that arrest itself might have a depressant effect on myocardial contractility.

Myocardial contractility, as measured by left ventricular function curves (the relationship between ventricular stroke work and filling pressure), was determined in normal dogs before periods of cardiac arrest induced by either potassium citrate, acetylcholine or aortic occlusion alone. Cardiopulmonary bypass was maintained with a rotating disc pump-oxygenator at flows of 100 ml./Kg./min. The periods of arrest varied between 10 and 30 minutes and the right heart was drained during the period of arrest and recovery. Twenty minutes following the restoration of coronary flow, left ventricular function curves were again examined. Arrest with either potassium citrate or acetylcholine for 20 or 30 minutes resulted in severe depression of myocardial function in 12 of 14 animals. Uninterrupted aortic occlusion of 20 minutes caused only minimal or moderate depression of contractility in 3 of 5 dogs. Intermittent anoxia, maintained for 30 minutes, did not produce severe depression in any of 5 dogs.

The studies indicate that intermittent aortic occlusion provides the advantages of a dry and quiet heart without causing subsequent impairment of myocardial function.

Familial Muscular Subaortic Stenosis

Lawrence B. Brent, Don L. Fisher, Pittsburgh, Pa., and William J. Taylor, Gainesville, Fla.

Subaortic stenosis has been regarded as a rare condition, usually caused by a fibrous ridge attached to the left ventricular myocardium below the aortic valve, and recently subject to surgical repair. It has not been recognized as a familial

disease. However, our recent experience suggests that there is another form of subvalvular stenosis which is caused by muscular hypertrophy, occurs with multiple cases in an affected family, requires special attention in differential diagnosis, and is not operable.

Our interest in subaortic stenosis was aroused by a patient in whom a clinical diagnosis of aortic stenosis was made, but at operation no aortic or subaortic stenosis could be demonstrated. The patient died postoperatively and at autopsy a "functional" muscular obstruction of the left ventricular outflow tract was found. Because of a strong history of heart disease and sudden death in the patient's family, a survey was made of the remaining members. Months later, an uncle of the patient who had been examined in the survey died suddenly and autopsy findings in the heart were identical with those of his nephew. A third patient was studied, unrelated to the first 2, but with similar clinical findings and a strong family history of heart disease. Six weeks later this patient, a 34-year-old housewife, also died suddenly at home. Autopsy revealed the same changes in the heart. Clinical and autopsy observations, and hemodynamic and operative data have been studied, along with the family pedigrees suggesting familial heart disease based on mendelian dominant inheritance.

Synthesis of Precordial Leads: Clinical Study of the Dipole Hypothesis of Electrocardiography

Stanley A. Briller† and Robert H. Okada, Philadelphia, Pa.

Torso model studies on 1 normal subject by Frank and cancellation and mirror image studies by others constitute the bulk of evidence in support of the dipole theory of electrocardiography and vectorecardiography.

Present studies are based upon a principle outlined by Becking: a consequence of dipole theory is that any body surface voltage must be capable of synthesis by linear combination of 3 other independent surface voltages. An electronic computer was constructed with which synthesis of multiple precordial voltages could be attempted by summing adjustable proportions of voltages at the right arm, left arm and left leg. The synthesized precordial voltage was electronically subtracted from the actual precordial voltage. The difference so obtained, expressed as a percentage of the actual precordial voltage, gave an index of the degree to which the dipole hypothesis failed to account for the observed precordial voltage.

In 23 normal subjects, the average index for each of 5 precordial locations was: V_1 , 13 ± 8 per cent, V_2 , 16 ± 11 per cent, V_3 , 15 ± 7 per cent, V_4 , 19 ± 11 per cent, V_5 , 13 ± 8 per cent. The smallest indices in this group (V_1 , 6 per cent, V_2 , 4 per cent, V_3 , 10 per cent, V_4 , 11 per cent, V_5 , 6 per cent) were obtained from the subject utilized by Frank in torso model studies. In 28 subjects with heart disease of various etiologies, values for the same precordial sites were: V_1 , 35 ± 30 per cent, V_2 , 38 ± 26 per cent, V_3 , 38 ± 14 per cent, V_4 , 31 ± 26 per cent, V_5 , 28 ± 23 per cent. These data indicate that in the presence of diseased (and occasionally healthy) myocardium, sizable voltages appearing on precordial electrodes frequently can neither be detected nor analyzed by theoretically perfect systems of vectorcardiography.

Detection and Measurement of Experimentally Produced Aortic Regurgitation

Leon Brotmacher, David E. Donald, Hiram W. Marshall, Richard J. Cheesman, and Earl H. Wood, Rochester, Minn.

Detection of indicator in the left ventricle immediately after injection into the aorta is proof of retrograde passage across the aortic valve. The fraction of dye regurgitated is related to the ratio of areas of curves (1) recorded from the left ventricle after equal successive injections of dye into aortic root and pulmonary artery, provided that forward flow remains unchanged and uniform mixing occurs; and (2) recorded simultaneously from left ventricle and femoral artery after injecting into the aortic root.

The regurgitant fractions were estimated in 25 control dogs and in 24 dogs, studied after production of aortic regurgitation by a closed-chest technique. Immediately thereafter, an independent estimate of regurgitation was obtained by direct measurement of backflow of blood through the valve, using pressure gradients recorded during life.

In 7 of 27 control studies, small amounts of dye were detected in the left ventricle after injection into aorta at the valve, the greatest regurgitant fraction being 0.04. This figure was exceeded in all dogs with aortic regurgitation. Varying the ascending aortic injection or left ventricular sampling sites and synchronizing the injection with systole or diastole did not affect regurgitant fractions critically. The correlation coefficient of regurgitant fraction values and percentage regurgitation determined from back perfusion studies was 0.85. The standard deviation of single determinations from the regression line

of 9 per cent regurgitation supports use of the method for estimation of regurgitation in individuals.

Other indicator-dilution methods frequently failed to detect regurgitation and were of no quantitative value.

Observations on Heparin-Activated and Physiologic Clearing Factor in Health and in Ischemic Heart Disease

David F. Brown, Albany, N.Y.

Excessive and prolonged alimentary lipemia associated with ischemic heart disease (IHD) may be due to some deficiency of the enzyme lipoprotein lipase, or clearing factor. This enzyme was measured in plasma from 25 healthy controls and 25 cases of IHD. Plasma obtained before, and 10 minutes after, intravenous heparin administration was incubated with a standard lipid emulsion (Lipomul). Clearing activity was measured by observing fall in optical density (as an index of triglyceride concentration) and by noting increasing concentration of nonesterified fatty acid (NEFA), with time. The presence of any inhibitor to clearing activity in the preheparin samples was also measured. Virtually no clearing activity was observed in the preheparin plasma from both groups and no inhibitor to clearing factor was detected. Postheparin plasma from the healthy and diseased individuals produced a considerable and equal decrease in the OD of the lipid emulsion and both groups produced a mean absolute increase in NEFA of 2 mEq/L. in a 90 minute period.

Simultaneous measurements of total esterified fatty acid (TEFA) and NEFA were also carried out in healthy individuals and in patients with IHD after a fat meal. While TEFA levels were higher at all times in the diseased group, a significant increase in NEFA concentration that also occurred after the meal differed little in the 2 groups. If this NEFA concentration can be considered an index of in vivo clearing activity, there would again seem to be no difference between the 2 groups.

The findings suggest that the abnormal alimentary lipemia associated with IHD can not be attributed to a deficiency of clearing factor.

Varied Response of Blood Lipid Levels to Altered Food Patterns

Helen B. Brown and Irvine H. Page, Cleveland, Ohio

Two years' experience with the effect of low-fat and vegetable-oil food patterns on serum lipids

of 34 patients shows that their abnormal serum lipid levels responded to dietary treatment according to the type of abnormality present. Serum lipid fraction studies demonstrate 3 distinct types of hyperlipemia: (1) hyperglyceridemia, in which triglyceride fraction is high relative to cholesterol level; (2) hypercholesteremia, in which cholesterol is elevated relative to triglyceride; and (3) mixed hyperlipemia, in which all serum lipids are elevated but are in normal proportion to each other.

In 8 of 9 hyperglyceridemic patients, all serum lipid levels dropped to near normal levels on the low-fat food pattern, yet the triglyceride levels were high relative to cholesterol. The highly variable serum cholesterol level not only became low but much more stable on vegetable-oil food pattern than on low-fat. However, 3 hyperglyceridemic patients, including 1 who did not respond to the low-fat food pattern, had higher serum cholesterol levels on vegetable-oil than on low-fat. In 15 hypercholesteremic patients serum lipid levels were less on either food pattern but did not attain normal levels in all patients. In 8, serum cholesterol did not drop below 350 mg. per 100 ml. In 10 mixed hyperlipemic patients, serum lipids dropped readily and remained at normal levels.

These results suggest that the physician with knowledge of the type of serum lipid abnormality may prescribe dietary treatment with reasonable assurance of the outcome.

Continuously Accelerating Decay of Indicator Concentration in Single Injection Dilution Curves

Richard A. Carleton, Gilbert E. Levinson, and Walter H. Abelmann,† Boston, Mass.

In the absence of shunts, exponential decay is considered characteristic of indicator-dilution curves. However, since concentration at a given instant is inversely proportional to flow, appropriately timed changes of flow should affect the decay limb.

Increases in flow induced shortly after injection produced continuously accelerating decay limbs of dilution curves in a model and in man.

With constant flow, the concentration decay accelerates until all detectable particles from proximal chambers have reached a final mixing chamber, at which time exponential decay begins. In a system without recirculation, ultimate exponential decay is inevitable. However, since discharge from a chamber is a function of its ejection/residual volume ratio, it may be predicted that, in a system with recirculation, diminution of this ratio in any proximal chamber may delay the onset of exponential decay beyond the appearance of recirculating indicator.

Continuously accelerating decay was encountered after injection into the right atrium in 8 of 11 consecutive studies of pulmonic stenosis and after injection into the right atrium and pulmonary artery in 5 of 11 studies of mitral stenosis, but only once in 31 consecutive normal subjects with the same injection sites.

These bowed curves, unlike those produced by acute increases in flow, should permit flow estimates after rectilinear semilogarithmic extension of the last 2 points before recirculation. Such estimates agreed closely with oxygen Fick value (mean difference = 0.4 L./min., S.D. 0.26).

Continuously accelerating decay limbs are applicable physiologic exceptions to the characteristic pattern of dilution curves.

Body Miscible Pool of Cholesterol in Man

Aram V. Chobanian and William Hollander, Boston, Mass.

With growing interest in the relationship between serum cholesterol levels and atherosclerosis, methods of measuring other aspects of cholesterol metabolism have become increasingly important. The present study was undertaken to determine indices of body cholesterol miscible pool and turnover rate in man.

A tracer dose of C^{14} -cholesterol was administered to 8 subjects and its disappearance from the serum followed for 3 months. In every case after a 4-5 week "equilibration" period when serum specific activity decreased relatively rapidly, the fall in specific activity approached an exponential rate, permitting calculation of body cholesterol turnover rate and miscible pool. The half-time disappearance of cholesterol in the group varied between 44 and 61 days and the miscible pool between 0.16 and 0.31 per cent body weight, comparable to values reported in other mammals.

Postmortem analyses of tissues in a subject who died of pulmonary infarction 20 days after isotope administration revealed the following relative cholesterol specific activities (serum = 1.0): red cells 1.0, liver 1.0, lung 1.1, adrenal 1.0, fat 0.8, heart 1.1, aorta 0.5, intestine 1.0, striated muscle 1.1, and brain 0.01. These data were consistent with the cholesterol disappearance curves and suggested that in 20 days, the C^{14} -cholesterol in all tissues other than the nervous system was either at or approaching equilibrium with serum cholesterol.

In conclusion: (1) useful indices of body cholesterol miscible pool and turnover rate may be obtained in man from isotopic studies; (2) with the exception of nervous tissue, cholesterol in all tissues studied, including aorta, appeared to be in the body miscible pool.

Reflex Control of Heart Rate Through Respiration: Laws Derived from Analog Computer Simulation

Manfred Clynes, Orangeburg, N.Y.

Normal and irregular respiration widely change the rate of the human heart from beat to beat. Dynamic mathematical relations describing respiratory sinus arrhythmia were derived through analog computer simulation. This was made possible through the use of dynamic data obtained from experiments designed with the aid of control theory.

If a signal proportional to thorax circumference is fed into the analog computer, the computer can calculate the complex heart rate changes in real time and record the output as a rate, along with that of the real heart. The close correspondence of the predicted and actual changes of heart rate for a wide variety of modes of breathing, and for different individuals, proves the validity of the nonlinear differential equations describing the phenomenon.

Individual variations are expressible in terms of the parameters of the equations.

The equations clarify the responsible neural and sensory processes. The respiratory effects are shown to be caused by 2 separate reflexes each producing biphasic heart rate transients in the same directions. The observed effects are the result of superposition of these transients. The variable and often paradoxical results previously observed in attempting to relate heart rate to respiration on a steady state, nondynamic basis are thus explained.

The laws indicate, as a consequence, that stretch receptors and not hemodynamic factors are responsible for initiating the changes in heart rate.

Circulatory Effects of Chronic Hypervolemia in Polycythemia Vera

Leonard A. Cobb and Robert J. Kramer, Seattle, Wash.

Polycythemia vera (PV) is characterized by a large total blood volume (TBV) and an increased red cell mass (RCM). Previous measurements of cardiac output (CO) in this disease have been limited to a few cases and have not been performed with presently available techniques.

Twenty-two measurements of CO were performed by T-1824 indicator-dilution curves and/or the Fick principle in 10 patients with PV. Studies were done when TBV and RCM were elevated and repeated 2 to 9 weeks later after reduction of TBV and RCM by phlebotomy. CO and blood volume (Cr^{51}) were measured in 10 suitable controls.

The average resting, supine cardiac index (CI) was increased to 5.00 L./min./M.² in the patients with PV (3.74 in controls). Stroke index (SI) in PV ranged from 51 to 74 ml. and in the controls from 37 to 48 ml. The pulse rate correlated poorly with blood volume. There was an excellent correlation between SI and TBV for all subjects ($r = 0.92$). Phlebotomies were associated with a consistent decrease in SI and CI. When measured, right atrial and "PC" pressures were normal in PV; "central blood volume" (pulmonary artery to brachial artery) was greatly increased in two patients with PV.

It is concluded, that in PV the resting stroke output of the heart is elevated in proportion to the increase in TBV. The mechanism for this regulating mechanism may be explained in part by an enhancement of heart volume, as proposed by Sjöstrand, and co-workers.

Prolonged Myocardial Anoxia and Atrioventricular Conduction

Jay D. Coffman, F. Bruce Lewis, and Donald E. Gregg, Washington, D.C.

Dogs were maintained on extracorporeal circulation, utilizing a donor dog and a Sigmamotor pump. Myocardial anoxia was produced by clamping the aorta (and pulmonary artery) above the origin of the coronary arteries. An empty heart was maintained by suction of both atria. Electrocardiograms were followed up to 5 hours after reperfusion of the coronary arteries for return of atrioventricular (A-V) conduction.

Ten experiments with myocardial anoxia, ranging from 6 to 100 minutes, showed return of A-V conduction. Two of 3 hearts anoxic for 120 minutes, and 1 of 3 anoxic for 150 minutes, recovered A-V conduction. One 165-minute anoxic heart failed to show a return of conduction. Five experiments with potassium citrate arrest of the heart after aortic clamping showed no beneficial effect on return of A-V conduction.

After approximately 90 minutes of myocardial anoxia with and without potassium arrest, the left, and subsequently, the right ventricle developed stiffness. By 120 minutes, the heart was irreversibly small and extremely firm, preventing an effective beat. Myocardial adenosine triphosphate (ATP) determinations after 120 minutes of anoxia showed an average decrease of 3.5 mM/Gm. in 8 hearts. Following reperfusion of 2 of these hearts, the ATP concentration failed to increase and even decreased in 120 minutes.

Canine A-V tissues can withstand complete anoxia up to 150 minutes with return of conduction but with severe myocardial damage, as evidenced by stiffness and defective ATP regenera-

tion. However, the period that conduction and myocardial tissue can survive anoxia varies with the individual dog.

Effect of Boundary Conditions on Ventricular Accession Potentials

Loyal L. Conrad and T. Edward Cuddy, Oklahoma City, Okla.

The effects produced by alterations in the boundary at the epicardial and endocardial surfaces on the ventricular potentials in the heart in situ in 10 dogs were studied. Boundary conditions were changed by opening and closing the chest, filling the thorax with saline-Hartman's solution, and injecting CO₂ into the ventricular cavities after intramural electrodes had been positioned. The effects on tangential components of accession were studied after extrasystolic stimulation of the contralateral ventricle and after right bundle-branch block.

The amplitude of R at all points from endocardial to epicardial surfaces was decreased by 70-100 per cent; at times the R became a notch on the downstroke of S by any measure which increased the conductivity of the medium surrounding the heart or which decreased the conductivity of the medium in the ventricular cavity. Measurements at the surface of the volume conductor were not made, but the potential at F was halved by filling the open chest with saline.

It is concluded that the progression in the amplitude of R from endocardial to epicardial surface is affected appreciably by the conductivity of the boundary media at the endocardial and epicardial surfaces of the ventricles.

Rapid Correction of Hyperlipemia and Hypercholesterolemia with Sulfated Alginic Acid

Paris C. Constantinides, Thomas C. Johnson, Brock M. Fahrni, and Hamish W. McIntosh, Vancouver, Canada

Sulfated alginic acid (Paritol), a sulfated polysaccharide with a mannuronic acid building block, was given under conditions of controlled caloric and lipid intake to 15 hospitalized cases of hyperlipemia (serum total lipid range 1,100-2,400 mg. per cent) and hypercholesterolemia (serum cholesterol range 280-600 mg. per cent) for periods from 5 days to 3 weeks. Serum total lipids, cholesterol, turbidity, and in most cases phospholipids, were determined daily throughout the treatment period, as well as during pretreatment and post-treatment control intervals.

This principle proved capable of extraordinarily rapid and intense action on the elevated serum

lipids, by both the intravenous and the intramuscular route. It normalized the total lipid values within 24 hours and the cholesterol values within 72 hours in 10 cases, while reducing them greatly within a slightly longer interval in another 4 cases. The antilipemic effect was sustained for the duration of treatment and it was only gradually reversed following withdrawal of the drug. The minimum effective cholesterol-depressing dose by the intramuscular route was found to be 2.5 mg./Kg./day. At this dosage sulfated alginic acid exhibited no anticoagulant action or side effects, and it displayed far greater antilipemic activity than equivalent amounts of heparin.

Thus, this substance has been found to attack most human hypercholesterolemias of myocardial infarction survivors with the same unparalleled speed and effectiveness it has shown in handling experimental rabbit lipemias.

Blood Pressure Reduction by Chlorothiazide

James Conway and Philip Lauwers, Ann Arbor, Mich.*

Chlorothiazide administered alone to 83 nonedematous hypertensive patients produced a significant fall in blood pressure (greater than 10 per cent systolic and diastolic) in 60 per cent of patients, the average fall being 23/15 mm. Hg. Patients with malignant hypertension and those with azotemia did not respond.

The cardiac index, measured in 16 patients on long-term therapy (more than 1 month), was 4.0 L. per minute as compared with 3.7 L. per minute in control period. The fall in blood pressure in these patients was 30/19 mm. Hg. It must be concluded, therefore, that chlorothiazide had produced an over-all reduction in peripheral resistance of 20 per cent.

The mode of action of chlorothiazide over long periods differs from its acute effects since a fall in cardiac output is regularly seen after 2 weeks of treatment, an average fall in output being approximately 25 per cent.

Effect of ACTH on the Plasma 17-21-Dehydroxysteroid Levels in Normotensive and Hypertensive Patients

David Y. Cooper, L. L. Johnson, J. C. Touchstone, and William S. Blakemore, Philadelphia, Pa.

Previous studies from this laboratory on patients subjected to adrenalectomy for hypertension indicated that cortisol formation of incubated adrenal tissue and cortisol output in the adrenal vein blood decreased with increasing severity of hypertension. To determine whether a similar relationship can be demonstrated in

peripheral blood, Porter-Silber positive steroids were measured with the Nelson-Samuels method in the plasma of 50 patients before and at the end of a 1 hour infusion of 10 μ g. of ACTH, and at hourly intervals for an additional 2 hours.

The 3 groups of patients studied had the following blood pressure ranges: (1) up to 135/90 mm. (20 patients); (2) 135/100 to 250/20 (20 patients); (3) above 250/120 (10 patients). Preinfusion levels in the 3 groups (10, 0.3 and 9.4 μ g. steroid per 100 ml. plasma) were similar, whereas the responses to ACTH differed significantly. In group 1, the response was linear with the highest values (28 μ g./100 ml.), occurring 2 hours after infusion. Patients of group 2 had 80-90 per cent of their maximal response (20 μ g./100 ml. plasma) at the end of the ACTH infusion. Group 3 patients had the smallest maximal response (12 μ g./100 ml. of plasma), occurring 1 hour after ACTH infusion.

These findings agree with the previous inference that the functional reserve of the adrenal declines in severe hypertension.

Inhibition of Cholesterol Biosynthesis in Man

Elmer E. Cooper, San Antonio, Tex.

Because liver adjusts cholesterol production in accordance with amounts returned in biliary-enteric circulation, inhibition of synthesis is necessary to reduce cholesterol concentration.

Reduction of endogenous cholesterol synthesis by specific inhibitor should therefore produce negative cholesterol balance and mobilize cholesterol from atheromatous plaques.

During uricosuric agent studies, benzmalecene, N-(1-methyl-2,3-di-p-chlorophenyl-maleamic acid (a-isomer), was discovered to inhibit cholesterol synthesis from C^{14} -acetate or C^{14} -dl-mevalonic acid by rat liver homogenates. Also, in chronic toxicity studies, in dogs, benzmalecene depressed cholesterol levels markedly, and hypercholesterolemia was inhibited in cholesterol fed chickens.

Benzmalecene proved effective in reducing serum cholesterol levels in 14 subjects (male and female, overtly atherosclerotic and normals) studied from 2 to 9 months.

The average cholesterol control for the group was 305.35 mg.; 500 mg. benzmalecene was administered in capsules before 2 or 3 meals daily (diet unrestricted). Compared to controls, an average drop of 93 mg. occurred the first week, 103 mg. the third week, 107 mg. the sixth, 96 mg. the twelfth, 63 mg. the twenty-second, 68 mg. the twenty-seventh and 100 mg. at the thirty-sixth week.

No toxic effects were observed in hematopoietic, cardiovascular or renal systems. Serum bilirubins, urobilinogens and alkaline phosphatases were normal. In several patients, there was an increase in bromsulphalein retention, with no jaundice and no bile salts in urine. The retention has been interpreted as functional inhibition of hepatic secretory transport mechanism for B.S.P. (enzymatic activity).

Cooperation and tolerance were excellent. In 1 instance there was an evanescent rash. Loose stools were encountered twice.

New Evidence of Cerebral Angiospasm

Eliot Corday and Sanford Rothenberg, Los Angeles, Calif.

Experiments were conducted on monkeys to determine if the larger cerebral arteries are able to contract. The arteries around the circle of Willis were photographed by new techniques through a window in the skull. It was demonstrated that cerebral angiospasm could be induced either by traumatic or electrical stimuli. When epinephrine was administered intravenously, it caused the larger arteries to contract as much as one third in diameter. This angiospasm could often be released by the local application of papaverine or Novocain or the systemic administration of norepinephrine. Carbon dioxide, which was believed to be a cerebral artery dilator, did not release the cerebral angiospasm. It was noted that the large arteries at the base of the brain are not affected by stimulation or interpolation of either the stellate ganglia or vagus nerves. Photographs of 1 human patient during surgery demonstrated that the local application of epinephrine caused angiospasm. It is concluded that cerebral angiospasm may result from a direct traumatic stimulus to the brain or from the systemic release of humoral substances.

Significance of Apparently Paradoxical Pressoreceptive Responses

Felix M. Cortes and Louis A. Soloff, Philadelphia, Pa.

During experiments with norepinephrine conducted for other reasons, it was noted that in some persons the heart rate did not change, while in others it quickened. Possible causes for these apparently paradoxical pressoreceptive responses were investigated in 34 consecutive cases of cardiac disease. Six had congenital, 5 coronary artery, 1 hypertensive, and 23 rheumatic heart disease. Fifteen were males, 19 females. The ages

varied from 20 to 72 years. In all subjects with congenital conditions and in 13 with rheumatic conditions, in 1 with hypertension, and in 4 with coronary artery disease, the heart rate was slower. Four with rheumatic heart disease had no change in rate. Five with rheumatic and the remaining 1 with coronary artery heart disease developed a faster rate.

The average rise in mean arterial pressure was 31 per cent for those who developed a slower rate, 26 per cent for those whose rate did not change, and 27 per cent for those whose rate quickened. These changes were related neither to the QT or Q_1 interval nor to ballistocardiographic changes in those on whom this study was done.

Fifty per cent of those whose heart rate slowed or did not change had been digitalized. Five of the 6 who developed a faster rate had been digitalized. The remaining 1 had dyspnea and recurrent arrhythmias which had not responded to previous digitalization.

Patients with increased heart rate and those with an unchanged rate were equally distributed throughout 4 decades. Of those who developed a faster rate, 1 was in the third, 1 in the fourth, 2 in the fifth, and 2 in the sixth decade.

Conclusion: 1. Cardiac disease can overwhelm the normal pressoreceptive response. 2. One must exclude cardiac disease before attributing abnormal baroreceptor response to aortic disease or to abnormalities of the baroreceptor. 3. The cardiac rate, in addition to the blood pressure, may act as a guide to optimal therapeutic doses of norepinephrine used to combat hypotensive states.

Mechanisms of A-V Block During High Rate and Wenckebach Periodicity

Paul F. Crane and Brian F. Hoffman, Brooklyn, N.Y.

Records of electrical activity of single myocardial fibers show that the delay in the passage of excitation through the A-V node depends upon a slow rate of depolarization in nodal fibers. Such fibers show steps or notches on the rising phase of the transmembrane action potential. Total dissociation resulting from acetylcholine results in a marked increase in slowness of depolarization and in temporal dispersion of the individual components of excitation which gives rise to the notches on the upstroke of these action potentials. Similar findings appear sufficient to explain first degree A-V block during high rate.

The mechanism of 2:1 block is more complex. The nodal action potential corresponding to the

blocked impulse occurs prior to completion of repolarization of the preceding nodal action potential. The blocked action potential is thereby decreased in rising velocity, amplitude, and duration. The decrease in duration of the blocked action potential permits full repolarization before the arrival of the next action potential (which propagates to the ventricle). This regular alternation in duration provides the basis for the regularity of the 2:1 rhythm. During Wenckebach periodicity, records obtained from a single fiber at the site of block show that both the increasing latency and ultimate block are associated with an increasing duration in the initial step of the action potential upstroke which reflects a progressively slower rise in that step.

Operation for Advanced Coronary Disease

Clarence E. Crook, Ann Arbor, Mich., Neal A. Goldsmith, Bend, Oreg., Enrique Garza-Falcon, Monterrey, Mexico, and Otto E. P. Seele, New Hanover, South Africa

A simple operation which incorporates the 2 main features of the Beck no. 1 operation is safe for advanced coronary disease patients.

Large procaine penicillin crystals placed in the pericardial sac produce excellent short-acting abrasion of epicardial and pericardial surfaces. Asbestos powder introduced with the penicillin acts as a chronic stimulant. These substances were insufflated into the pericardium in a large series of dogs. Two hundred and forty operations as pilot studies and tests showed this procedure to be safe, simple, and highly effective. Of the animals on which insufflation had been done, 76 per cent survived ligation of the anterior descending coronary artery, while only 32.2 per cent of normal dogs survived such ligations. Following coronary ligation, blood transaminase levels were lower and myocardial infarcts were smaller in the animals previously insufflated with penicillin and asbestos than in normal controls.

The insufflation operation, performed through 2 inch extrapleural incisions on 5 middle-aged males who had coronary disease and disabling angina, resulted in return to work of all 5 males and complete relief of pain in 4. Penicillin and asbestos, suspended in a special aqueous formula and tested with 70 laboratory operations, was injected into the pericardium of 23 dogs. Two weeks later coronary artery ligations resulted in 18 (78.7 per cent) survivors.

The penicillin-asbestos suspension, now prepared for human use, will become commercially available at the completion of the current human case study.

Hydrochlorothiazide: Clinical Evaluation in Congestive Heart Failure, Hypertension and Laennec's Cirrhosis

Norman A. David, George A. Porter, and Warren S. Welborn, Portland, Ore.

Hydrochlorothiazide (Esidrix) was tried in 75 ambulatory and 19 hospitalized patients. Diagnoses for the outpatients were: hypertension, 31; hypertension with congestive heart failure, 15; congestive heart failure, 24; premenstrual tension, 2; Laennec's cirrhosis, 3; and Gaucher's disease, 1. Doses used were 75-125 mg. per day. Fifty-six patients were treated for periods of from 4 to 6 months. Good diuresis was noted initially in edematous patients and in satisfactory lowering of the blood pressure in the hypertensives. Supplemental potassium was added about the fourth to sixth week of trial in the majority of patients. Serum electrolytes studied at monthly intervals showed few abnormal changes; in 2 patients with serum chloride values of 94 and 79 mEq. after 2 month's trial, the drug was stopped. Side effects were: nausea, 9; confusion, 1; paranoid delusions, 1; and peculiar small petechial hemorrhages, nonpruritic, on the arms, legs and chest, 2.

Diagnoses for the 19 hospitalized patients were: Laennec's cirrhosis, 9; congestive heart failure, 9; and nephrosis, 1. Responses were considered excellent in 7, good in 5, fair in 2 and poor (failure) in 5. Esidrix alone was used in 8 patients, while various combinations of Esidrix, Diamox, or chloride "loading" and mercurial injections, and/or steroids were tried in 11 patients. Dosage of hydrochlorothiazide was 75-150 mg. per day, given for periods of from 4 to 20 days. Since supplemental potassium was used, the most frequently noted electrolyte change was an elevated serum bicarbonate. No serious untoward effects were seen.

Pathologic Anatomy of the Mitral and Aortic Valves, with Particular Reference to Surgical Corrective Technics and Possibilities of Prosthetic Replacement

Julio C. Davila and Robert P. Glover, Philadelphia, Pa.

Gross studies of numerous specimens of valvular heart disease by the usual pathologic technics and by direct and cinematographic observations on the pulse duplicator have led the authors to describe valvular pathology in relation to the altered mechanics of those structures. Based on more than 1,500 operations for valvular heart disease, on the anatomic and pathologic studies, and on animal experiments in efforts to develop suitable valvular prosthetics, an evaluation of

current surgical concepts and of directions for surgical research was made.

Surgical Treatment of Mitral Insufficiency: Evaluation of Late Results of Circumferential Suture of the Annulus

Julio C. Davila and Robert P. Glover, Philadelphia, Pa.

During the past 4½ years, 70 cases of pure or predominant mitral insufficiency have been treated by circumferential suture of the mitral valve (mitral purse-string). The last 15 cases have been operated without mortality. Thirty-seven are living, in June 1959, 3 months to 4½ years postoperatively. Thirty-one of these patients are more than 1 year postoperative. This work reviews the clinical material with particular emphasis on types of cases treated, evaluation and criteria for selection of surgical candidates, operative risk, and immediate and long-term results.

Intractable Angina Pectoris with Obliterating Coronary Arteriosclerotic Heart Disease in Man Treated by the Operation of Left Atrial-Pulmonary Artery Anastomosis

Stacey B. Day, Minneapolis, Minn.

Our previous experimental studies presented objective evidence to indicate that a right-to-left extracardiac shunt between the pulmonary artery and the left atrium was a potent stimulus to the development of interarterial intercoronary anastomoses. If such a fistula be of appropriate size and pressure differentials be small, the circulatory hemodynamics provide a peripheral arterial oxygen saturation ranging from 75-90 per cent unaccompanied by the unfavorable cardiac enlargement, high pulse pressure, increased cardiac output, and other malevolent sequelae of systemic arteriovenous fistulas. In view of these studies, confirming a marked coronary vasodilation in response to hypoxemia, it was deemed justifiable to investigate the above described method of redistributing the blood supply to the ischemic myocardium in man, providing that it could be demonstrated that coronary inflow was impaired by obliterating arteriosclerotic heart disease. To date, 3 patients with classical histories of angina pectoris, unrelieved by medical therapy and accompanied by intolerable pain, rendering them unable to work, have been operated upon. In all cases, objective evidence of severe obliterating disease was established by preoperative coronary arteriography. Dramatic and sustained relief of pain, improvement in health and early return to gainful employment have followed operation in each case. There has been no postsurgical mor-

bidity. Cardiomegaly has not been observed in the longest follow-up to date (6 months). In no case has the shunt been closed. It is suggested that the method will need longer trial here and in other hands to evaluate precisely its advantages and limitations.

Dissecting Aneurysms of the Aorta: Critical Analysis of 47 Cases Treated Surgically

Michael E. De Bakey, Denton A. Cooley, E. Stanley Crawford, and George C. Morris, Jr., Houston, Tex.

This report is concerned with certain observations derived from an analysis of 47 cases of dissecting aneurysms of the aorta in which surgical treatment was employed during a period of a little over 5 years. In addition to certain clinical features, particular emphasis is placed upon the wide variations in the morphologic aspects of the disease from well localized lesions, sometimes multiple, to extensive involvement of virtually the entire aorta. These variable pathologic characteristics are believed to be particularly significant in relation to the different methods of surgical treatment which may be employed. Certain factors appear to have a significant bearing upon operative mortality. Follow-up studies, including aortography in some, have been made on all 34 patients surviving operation and indicate highly gratifying results.

Double-Catheter Dye-Dilution Technic

Arthur C. DeGraff, Jr., Albert L. Hyman, and Antonio C. Quiroz, New Orleans, La.

The double-catheter dye-dilution technic, similar to that employed by Wood et al., for localization and quantitation of intracardiac shunts, has been employed in 30 patients. Known quantities of indocyanine green dye are injected into a distal pulmonary artery as blood is simultaneously withdrawn through densitometers from the main pulmonary and systemic arteries. Early appearance of the dye in the MPA indicates the presence of a left-to-right shunt. Successive withdrawals of blood from progressively more proximal chambers until early recirculation is no longer seen, localizes the site of the shunt. Dye curves are then obtained from pulmonary and systemic arteries after inferior vena caval injection. Similarly, right-to-left shunts which are thus uncovered may be localized.

Pulmonary blood flow is calculated from the Hamilton-Stewart formula, using the area of curve obtained from injection into cava and withdrawal from pulmonary artery. The left-to-right shunt

is calculated from the ratio of the curve from the injection into a distal pulmonary artery and withdrawal from the main pulmonary artery, and the cava to pulmonary artery curve, in the Hamilton-Stewart formula. Right-to-left shunts are similarly calculated.

Model experiments indicate that the femoral artery forward triangle of Hetzel cannot be used with confidence in estimation of pulmonary blood flow at higher shunt rates. With larger shunt dye recirculated through the shunt reaches the periphery before the peripheral dye curve peaks. Calculations from the O_2 and IVC to PA method were only similar to the forward triangle method when shunts were less than 2.5 times systemic venous return.

The dye method is simpler than the O_2 method and gives a sharp, accurate and immediate endpoint. Shunts as small as 4 per cent of systemic flow, undetected by the O_2 method but established easily by dye dilution technique, have been surgically proven.

Studies on the Fibrinolytic System and the Use of Fibrinolysin in Acute Myocardial Infarction: Preliminary Report

Antonio C. deLeon, Washington, D.C., Samuel Bellet, George Tsitouris, and Herschel Sandberg, Philadelphia, Pa.

Because of the recent interest in the use of fibrinolysin in the treatment of thromboembolic disease, the following studies were performed: 1. plasmin and antiplasmin activity determinations in a group of 28 normal subjects and in 30 cases of acute myocardial infarction (17 without heparin and 13 with heparin), 2. the use of fibrinolysin in the treatment of acute myocardial infarction (8 cases). Plasmin titers were determined by the whole clot lysis time, using lysis within 20 minutes or less as an indication of significant fibrinolytic activity. Antiplasmin levels were determined by the clot lysis time produced by 0.2 ml. of 1:10, 1:20, and 1:40 dilutions of 2,000 units of Merck plasmin per milliliter on a preformed clot in the presence of the patient's undiluted plasma. No plasmin activity was noted in either the normal or the acute myocardial infarction groups. The antiplasmin level of the normal group was 211 ± 47 seconds (1:10); 463 ± 146 seconds (1:20); $755 \pm 191 \pm 1$ 1,200 seconds (1:40); the group of myocardial infarction without heparin was 440 ± 231 (1:10); $857.0 \pm 7 > 1,200$ seconds (1:20); $1,095.1 \pm 11 > 1,200$ seconds (1:40); and the group of myocardial infarction with heparin was 364 ± 105 seconds (1:10); $823.7 \pm 3 > 1,200$ seconds

(20); $1,086.8 \pm 9 > 1,200$ seconds (1:40). It will be noted that the group of acute myocardial infarction taken as a whole have antiplasmin levels significantly higher than the normal controls. Human plasmin in doses ranging from 1,000 to 200,000 units was infused intravenously in 8 cases of acute myocardial infarction. Three of the 8 developed pyrexia of over 101 F. and 2 showed a rise in temperature of 1 degree F. with infusion of the drug. Other side effects encountered were chills, mild transient hypotension, nausea, vomiting and flushing. Six of the 8 cases had striking relief of angina and 3 showed improvement of the electrocardiogram after plasmin infusion. These results suggest that fibrinolysin may be an important addition to the armamentarium of therapy in selected patients with acute myocardial infarction.

Acidosis in Clinical and Experimental Hypothermia Following Total Circulatory Occlusion

Andreas D. Demetriades, R. Adams Cowley, Paul Hackett, Frieda Rudo, and Samuel Bessman, Baltimore, Md.

Total circulatory occlusion and release is similar to the "stop flow" technic used in study of renal physiology. Following a period of cessation of circulation to the brain and the peripheral tissues, the composition of the first venous blood flow through these tissues upon release of the occlusion should reflect the changes which occurred during the occlusive ischemic period. The venous blood would be the more accurate index for a particular organ than the arterial blood since arterial blood represents considerable dilution. Samples of peripheral venous, jugular and arterial blood were taken prior to occlusion and 1, 5 and 10 minutes after release under the following circumstances: 1. Clinical: Patients undergoing cardiac surgery at 27-26 C. and occlusion periods from 3-14 minutes. 2. Experimental: (a) the standard preparation was cooling the dog to 25 C. with total inflow occlusion for 10 minutes, (b) control at normothermia. A marked acidosis developed during occlusion, more striking in the brain than in the peripheral blood. This was accompanied by elevation in CO_2 and in lactic acid content, the former being more significant in the brain and the latter in the peripheral samples. It is felt that the lactic acid accumulates from the periphery and may be the result of failure of removal by the liver. The acidosis in brain tissue was felt to be due to the great excess of CO_2 . A possible source of the O_2 is the decarboxylation of glutamic acid to form γ -amino butyric acid + CO_2 .

Considerations of the Pathology and Anatomy of Superior Mesenteric Artery Insufficiency

John R. Derrick, A. Ray Remmers, and Harry E. Sarles, Galveston, Tex.

This study has been directed toward an evaluation of the relationship, based on preliminary evidence, between the pathologic status of the superior mesenteric artery and clinical symptomatology.

Three hundred and seventy-five superior mesenteric arteries, secured at necropsy, have been studied in detail. Each vessel was measured with fine calipers at 3 specific sites to confirm the pattern of arteriosclerotic involvement. Thirty-seven per cent of the unselected specimens examined demonstrated some degree of narrowing of the superior mesenteric artery. The degree of narrowing varied from 12 to 86 per cent of the predicted normal cross-sectional area, with an average of 28 per cent narrowing. From these data, we can conclude that significant diminution in the cross-sectional area of the superior mesenteric artery is a common finding in pathologic specimens.

A review of the clinical charts of patients dying with superior mesenteric artery occlusion suggests that clinical evidence of insufficiency may precede the acute occlusion by months or years. The clinical material seems to demonstrate that many physiologic derangements may precipitate episodes of acute occlusion, such as a significant drop in the blood pressure, changes in the blood viscosity, and vigorous abdominal palpation.

A technic of selective visceral arteriography has been developed as a means of demonstrating isolated changes in the superior mesenteric artery. Extensive clinical, laboratory, pressure relations, and operative findings have been evaluated in 2 patients.

Quinidine's Cardiac Toxicity, a Triad

H. Lenox H. Dick and Elton L. McCawley, Portland, Ore.

Despite 30 years' experience with quinidine, its toxic reactions are poorly understood. Our observations suggest that quinidine's toxicity involves 3 or more mechanisms. Ventricular tachycardia is a reported cause of death during quinidine therapy. Yet in dogs, death from quinidine is accompanied by bradycardia with broad, low-voltage waves (slowed depolarization). When, however, the right or left bundle is severed, doses of quinidine in the therapeutic range provoke an apparent ventricular tachycardia. Direct atrial leads reveal the tachycardia to be supraventricular in origin for P waves are present; the wide QRS due to bundle-branch block gives the appearance

of ventricular tachycardia. Review of the electrocardiograms of selected patients developing "ventricular tachycardia" given quinidine indicate a pre-existing intraventricular conduction disturbance.

Quinidine is also hazardous for patients with extreme cardiomegaly and congestion. Suspecting a role of the liver, its blood supply was ligated in dogs with a portal-caval shunt made to avoid portal hypertension. Dogs so treated tolerated only a fraction of the usual lethal dose of quinidine. The times involved were too brief for significant liver metabolism of quinidine but electrolyte changes are implicated.

Bellet demonstrated the effectiveness of sodium lactate reversal of electrocardiographic changes of toxic doses of quinidine. Confirming this, we noted also an elevation of blood pressure and respiration. That the effectiveness of sodium lactate depends on reversing quinidine's acidosis is supported by experiments where respiratory alkalosis (tank respirator) reverses but respiratory acidosis (inhaled CO_2) may exaggerate quinidine toxicity.

Venoarterial Pumping for the Relief of Experimental Pulmonary Hypertension

James F. Dickson, III, James W. Dow, and Neil A. J. Hamer, Philadelphia, Pa.

In potentially reversible conditions with a diminished cardiac output, such as myocardial infarction, massive pulmonary embolism, and intractable congestive heart failure with a surgically correctable lesion, mechanical support of the circulation may be useful.

A closed system for withdrawing blood by gravity from the superior vena cava and pumping it into the aorta at the bifurcation by means of peripheral cannulation has been employed in the dog for as long as 52 hours and clinically for 26 hours without ill effect. The splanchnic bed is perfused in part by oxygenated blood from above and by shunted blood from below. The system recalls the fetal condition in that partially oxygenated venous blood from the upper body perfuses the lower distal capillary bed before returning to the lungs for reoxygenation. The procedure increases or does not change total body perfusion, and tends to reduce cardiac output and raise aortic mean pressure.

In a series of experiments, pulmonary hypertension was produced by chronic mitral insufficiency, pulmonary embolism and constant serotonin infusion. Venoarterial pumping was shown to decrease flow and pressure in the pulmonary circuit and increase systemic flow and arterial pressure. These results suggest that the procedure

might benefit patients in shock and pulmonary edema following massive myocardial infarction and pulmonary hypertension due to pulmonary embolus.

Pressure-Volume Curves of the Diastolic Left Ventricle in Man

Harold T. Dodge, Donald H. Ballew, and Harold Sandler, Seattle, Wash.

Diastolic left ventricular pressure-volume (P-V) curves in man with heart disease of varying etiologies have been determined in 5 subjects. Volumes have been calculated from biplane angiocardigrams. A photocell recorded time of each x-ray exposure with reference to the electrocardiogram and arterial pressure in all subjects, and left ventricular or left atrial pressure in 4 subjects. Simultaneous left heart pressures were recorded through a catheter inserted in the left heart. In 1 subject, left heart pressures were recorded just preceding angiocardiology.

A method for calculating left ventricular chamber volumes from biplane x-rays has been developed from 84 observations on 9 postmortem hearts over a 25-350 ml. volume range and differing left ventricular rotations and positions with a standard error of estimate of ± 8.1 ml.

Left ventricular time-pressure-volume curves were determined from a composite of the diastolic portion of 3-4 beats. Range of volumes varied in the subjects (16-115, 37-240, 105-250, 290-345, and 235-450 ml.), with large ventricular displacement volumes observed in subjects with valvular insufficiency. Diastolic pressures ranged from 0-60 mm. Hg. Attempts to superimpose individual diastolic P-V curves to arrive at an over-all P-V curve over the 16-450 ml. and 0-65 mm. Hg. ranges reveal that the P-V characteristics of individual hearts differ. This variation may be a consequence of type or duration of heart disease. Individual curves showed filling pressures as low as 6 mm. Hg with volumes approaching twice normal, and considerable volume variation for a given elevated filling pressure.

Production of Shock by Blood Volume Exchange in Dogs

James W. Dow, James F. Dickson, III, Neil A. J. Hamer and Howard L. Gadbois, Philadelphia, Pa.

Exchange of as little as 200 ml. of homologous blood without altering intravascular volume may produce a shock state featured by the sequestration of blood in the liver and portal venous system. Blood fractionation has shown the shock to be produced by the plasma.

This syndrome has been investigated in a series of 114 experiments involving homologous blood exchange. It is characterized by: (1) hepatic engorgement and acute portal hypertension, (2) reduced venous return, and (3) profound arterial hypotension. The acid-base and electrolyte disturbances have been outlined. Apparent hemodynamic and metabolic recovery occurs in 40 to 60 minutes. Resumption of blood exchange does not reproduce the collapse. The syndrome has appeared in 29 per cent (25 of 86) of procedures involving a single donor, and in 61 per cent (17 of 28) where multiple donors were used. A similarity to the early anaphylactic phase of endotoxin shock has been noted and comparisons made.

Reactions of this type have complicated experimental heart-lung bypass leading to misunderstanding of the effects of perfusion and delaying clinical open heart surgery. Experimental investigations involving homologous blood replacement may be misinterpreted if the effects of this syndrome are not recognized.

Detection of Early Renal Impairment in the Hypertensive Patient

Leonard S. Dreifus, Frank DeMaio, Philip Lisan, and Joseph Rosenfeld, Philadelphia, Pa.

The presence and severity of kidney disease is frequently difficult to evaluate in hypertensive patients without renal hemodynamic studies, and studies of glomerular filtration rate and renal plasma flow (GFR and RPF).

This study correlates the relatively simple method of osmolar concentration ratio of the urine and plasma (Uosm/Posm), as measured by the freezing point, with inulin, creatinine and PAH clearances. Seventy-five hypertensive patients were selected solely on the basis that the usual laboratory tests of renal function (urinalysis, concentration tests of specific gravity, BUN, creatinine, and PSP) were normal or indeterminate.

Urinary osmolar concentration was impaired (< 800 mOsm/Kg.) in 61 (82 per cent) patients (mean blood pressure, MBP, 139.0 ± 1.8 mm. Hg) and normal in 14 (18 per cent) patients (MBP 131.2 ± 4.4 mm. Hg). Further definition of renal function, utilizing GFR and RPF, correlated well with Uosm/Posm. In 5 instances, Uosm/Posm suggested impaired concentration in the face of normal GFR and RPF.

Abnormalities of the electrocardiogram, cardiac size, and optic fundi were in keeping with the degree of renal impairment. In 50 patients with abnormal Uosm/Posm, the electrocardiogram and cardiac size were abnormal. Of the 14 patients with normal Uosm/Posm, only 4 demonstrated other vascular abnormalities. Following antihyper-

tensive therapy (6-8 months) there was no significant improvement in Uosm/Posm or GFR. In some instances, there was definite deterioration initially with a tendency to return to pretreatment levels laterally. The maximal Uosm/Posm under hydropenic conditions paralleled GFR and RPF and may be used as a simple, rapid quantitative test of renal function in hypertensive patients where the presence of renal disease is not suspected by ordinary studies.

Pitfalls in the Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

Leonard S. Dreifus, Philadelphia, Pa.

In a majority of instances, the electrocardiogram reflects the diagnosis of left ventricular hypertrophy (LVH) and is in keeping with the cardiac hemodynamics and size. However, there appear to be a certain number of discrepancies between the clinical and electrocardiographic findings. Furthermore, there are variations in progression and retrogression of LVH patterns without obvious alterations of hemodynamic or myocardial factors. This study attempts to analyze the causes contributing to the erroneous diagnosis of LVH by the electrocardiogram.

Eleven patients were selected in whom the electrocardiographic diagnosis of LVH was made by only the most strict criteria of Sokolow and Lyon (typical RS-T changes of LVH in association with high QRS waves in limb, aV limb, and precordial leads). In all instances the possibility of valvular, hypertensive or congenital heart disease was ruled out by sequential examinations at 2-3 year intervals and appropriate hemodynamic studies. In 5 patients, definite and progressive coronary artery disease was present, 2 patients were psychotic, 1 individual was a professional athlete, and 3 were average. In all instances the electrocardiograms were interpreted as LVH by at least 2 electrocardiographers.

The possible reasons for the misinterpretation of the electrocardiogram as LVH in the face of normal hemodynamics and cardiac size can be summarized as follows: (1) coronary artery disease; (2) abnormalities in the time and sequence of intraventricular conduction; and (3) a disproportional disturbance in the activation times of the right vs. the left ventricles.

Coronary Pericarditis

William Dressler, New York, N.Y.

The term "coronary pericarditis" is used to denote a condition which develops secondary to arteriosclerotic heart disease. Large or small

areas of ischemic myocardial necrosis seem to be the determining factor. Pericarditis is almost invariably associated with pleuritis and often with pneumonitis. A tendency to relapse is a characteristic feature of the syndrome.

When pericarditis is preceded by a dramatic well-defined myocardial infarction, the causal relationship is obvious and the diagnosis is readily made. When, however, the acute coronary episode is mild or silent, and there is a lapse of many weeks between the coronary attack and recognition of pericarditis, the causal relationship is obscured and the condition presents a puzzling diagnostic problem. Idiopathic pericarditis is readily diagnosed. Ten instances of this type, including 2 postmortem examinations, were observed by the author.

Search for etiology in any given case of pericarditis should include, among other causes, "coronary" origin. Diagnostic considerations of this kind will result in separation of a number of cases hitherto assigned to idiopathic pericarditis and in a reduction of this undesirable group.

Effects of Hypoxia on Peripheral Venous Tone in Man

John W. Eckstein† and A. W. Horsley, Iowa City, Iowa

Nine normal men were studied while supine. Forearm venous-pressure volume curves were obtained by a plethysmographic method. Observations on venous tone, venous pressure, arterial oxygen saturation (ear oximeter), and endexpiratory CO₂ tension were made after subjects had breathed air and 12 and 8 per cent oxygen in nitrogen for 8 minutes.

Arterial oxygen saturation averaged 98, 78, and 54 per cent while breathing air and 12 and 8 per cent oxygen respectively. Corresponding values for endexpiratory CO₂ tension were 41.4, 39.6 and 37.2 mm. Hg. Low oxygen breathing had no consistent effect on venous pressure. There was no change in venous tone with the 12 per cent mixture. However, active venous constriction occurred regularly with 8 per cent oxygen. Forearm venous volume at a transmural pressure of 30 mm. Hg averaged 4.3 ml./100 ml. of tissue with air, and 3.8 ml. with 8 per cent oxygen ($p < 0.001$). This degree of venous constriction was sufficient to "push" significant amounts of blood from the extremity. The naturally occurring forearm venous blood volume averaged 3.1 ml./100 ml. with air and 2.8 ml. with 8 per cent oxygen ($p < 0.001$). This venous constriction could not be attributed to hyperventilation since voluntarily overbreathing (air) to the same endexpiratory CO₂ level observed with 8 per cent oxygen did not alter venomotor tone.

The shift of blood from the peripheral veins may help to explain the pulmonary hypertension and hyperemia which occurs with hypoxia.

Factors Influencing Results in the Surgical Treatment of Patients with Cardiac Septal Defects

Johann L. Ehrenhaft, Montague S. Lawrence, Ernest O. Theilen, June M. Fisher, and William R. Wilson, Iowa City, Iowa

The mortality in the surgical treatment of 26 patients with atrial and ventricular septal defects was 10 per cent for the entire group. All of the deaths occurred in patients who had complicated defects or grossly abnormal physiologic changes such as pulmonary hypertension. Seven of seven patients with atrial defects were operated upon using hypothermia alone. Valvular pulmonary stenosis or partial anomalous pulmonary venous connections did not increase the hazard of the procedures. Deaths in the hypothermia group resulted from early attempts to repair ostium primum defects and in some patients with pulmonary hypertension. Eighteen patients with atrial defects were operated upon using an extracorporeal circuit. Six of these had ostium primum defects and 1 also had total anomalous venous return.

One hundred and thirty patients with ventricular septal defects have been operated upon using a pump-oxygenator. All of the patients with isolated and uncomplicated defects (68 patients) survived. Deaths occurred in patients with severe pulmonary hypertension and when associated abnormalities were present such as infundibular stenosis or aortic valvular insufficiency. The risk was significantly higher in the cyanotic group. Factors related to the increased morbidity and mortality in this group were: the length of perfusion, insertion of plastic prosthesis, rhythm disturbances, postoperative respiratory complications, and occasionally, cerebral or coronary air embolization. Poor postoperative results in the surviving group have occasionally been due to partial reopening of the defects or aortic insufficiency. Preoperative diagnostic errors may occur in ostium secundum versus ostium primum defects, left ventricular-right atrial shunts and in patent ductus arteriosus with pulmonary hypertension and pulmonic valvular insufficiency.

Infundibular Pulmonic Stenosis without Septal Defects

Johann L. Ehrenhaft, Ernest O. Theilen, June M. Fisher, and William R. Wilson, Iowa City, Iowa

Infundibular stenosis as an isolated entity is relatively rare. We have operated upon 6 patients

with this lesion, 1 of whom had associated valvular stenosis. The physical signs are not diagnostic and the systolic murmur may be confused with that of an interventricular septal defect. The pulmonic second sound is usually diminished. Electrocardiographic findings show systolic overload type of right ventricular hypertrophy. Radiographic studies may or may not reveal poststenotic pulmonary artery dilatation depending upon the anatomic relationship of the infundibular stenosis to the pulmonic valve ring. The pulmonary vasculature is normal or decreased. Angiocardiography may be of diagnostic help. At cardiac catheterization, right ventricular pressures are high. A transitional pressure zone or a distal ventricular chamber with reduced pressures may be shown depending upon the location of the muscular stenosis. Systemic arterial saturation studies are normal.

Surgical correction was accomplished in 3 patients using hypothermia and in 3 using an extracorporeal circuit. The pump-oxygenator is preferred over hypothermia for the following reasons: The diagnosis may not always be correct, and a masked ventricular septal defect may be present. It permits more time for an adequate resection with less risk of damage to other intracardiac structures. It permits ligation of relatively large intramural coronary arteries which may be opened during the resection. These could act as coronary artery-right ventricular shunts. Complete resections of the infundibular muscular mass should abolish or markedly decrease the preoperative pressure gradients.

Metabolic Studies with Radioactive Heparin in Humans

Harold B. Eiber, Isidore Danishefsky, Frank J. Borrelli, and Joseph Litwins, New York, N. Y.

By employing radioactive heparin (labeled with S^{35}), a study was made on the fate of heparin with regard to clearance from blood and urinary excretion after intravenous injection into human subjects. It was found that the heparin is removed from the bloodstream within 4 hours and that the change in clotting time parallels closely that of the loss of radioactivity from the blood.

Injection of 50 mg. of heparin results in the urinary excretion of the radioactivity in the form of inorganic sulfate, indicating that heparin is desulfated during normal metabolic processes. When larger doses (75 mg.) are administered, a portion of the heparin (20 per cent) is excreted unchanged or only partially desulfated. It is thus demonstrated that the human is capable of converting the polysaccharide-linked sulfate of

heparin into inorganic sulfate. However, the capacity of the organism to perform this degradation is limited, so that when higher doses are administered a portion of the material is excreted undegraded.

Administration of heparin- S^{35} as a sublingual tablet containing 15 to 30 mg. of heparin results in the excretion of only a minute amount of radioactivity (less than 2 mg. in terms of heparin) in the urine. There was no proportionality found in these studies between the amounts administered and absorbed, and on the basis of the actual quantity of heparin passing through the bloodstream it would not be expected to have any pharmacologic effect.

Measurement of Central Blood Volume by External Monitoring

Robert H. Eich, William R. Chaffee, and Robert B. Chodos, Syracuse, N.Y.

The use of external monitoring to measure central blood volume (CBV) was evaluated in 46 hospitalized subjects. Radioactive human serum albumin was injected through a catheter in the right axillary vein. Cardiac output was measured by the Hamilton-Stewart method, sampling from the left brachial artery. Duplicate determinations were done 10 minutes apart.

A scintillation detector with a 1 inch crystal was used, combined with a radiation analyzer and scaler. The scaler was modified to record count frequency on an oscillographic tracing. In 29 patients the counter was centered over the heart, 9 being studied with high degree of collimation and 20 with minimal collimation. Seventeen subjects were studied using duplicate counting equipment, 1 counter over the right heart, and 1 over the apex.

In the single counter study, CBV was determined as the product of cardiac output and the time between the right and left peaks. With the dual counters, a right and left slope could be determined, and thus a mean circulation time for each side could be used in the calculation. With the single counter the CBV was 407 ml./M.² (S.D. ± 107) without collimation, and 446 ml./M.² (S.D. ± 80) with collimation. The arterial CBV was 1,260 ml./M.² (S.D. ± 161). Using the dual counters, the CBV was 436 ml./M.² (S.D. ± 62). The major change in the slope of the dye curve occurred between the right and left side, right slope being 0.52, left 0.26, and arterial 0.22.

By measuring a smaller volume without increasing the variability, external monitoring would appear useful in the study of CBV.

Left Heart Catheterization: A Critical Evaluation of the Data in Patients with Mitral Stenosis and Insufficiency

Myrvin H. Ellestad and Chi Kong Liu, Torrance, Calif.

The several procedures used in left heart catheterization are now well standardized, but the interpretation of the data is often confusing. After careful evaluation of over 40 cases studied in our laboratory and review of the literature on this subject, several important points require emphasis: The relative risk between the transbronchial and the percutaneous approach has been overemphasized and the hazards of either procedure are much less than that of thoracotomy. Left heart catheterization should be used whenever the degree of stenosis and insufficiency is in doubt on a clinical basis. While it is advisable to obtain the diastolic pressure in both the left atrium and ventricle, sometimes this cannot be done, especially by the use of transbronchial approach. When only atrial pressure is available for analysis, the atrial pressure during diastole and its pattern, as well as the height of the A wave gives information for either significant stenosis or insufficiency. The various formulas proposed previously are of limited value. The slow and gradual rise in the ventricular diastolic pressure may indicate significant stenosis. The use of intracardiac phonocardiographic technics in conjunction with pressure curves has some ancillary value.

Effect of Vasopressors on Murmurs of Unknown Origin and of Organic Heart Disease

Myrvin H. Ellestad and Chi Kong Liu, Torrance, Calif.

The clinical diagnosis of murmurs which are functional in nature or of unknown origin has long been one of the most difficult problems. Often children are referred and followed in clinics year after year while physicians wait for disappearance of heart murmurs or for other signs to develop which warrant doing more complicated procedures such as cardiac catheterization. A simple method for a more accurate differential diagnosis is much needed.

Since functional murmur tends to be associated with an asthenic habitus with low peripheral resistance, it was felt that the use of vasopressors such as levarterenol intravenously or Vasoxyl intramuscularly to increase the peripheral resistance may abolish or modify functional heart murmurs.

A series of 20 cases with proved organic lesions were used as controls and 30 cases of suspected functional murmur were studied before

and after vasopressors. In patients with organic heart disease there was little or no change in the character of systolic murmurs.

Of the group with suspected functional murmur: Systolic murmurs have either decreased or disappeared in 43 per cent of the cases. No apparent change of murmurs in 28 per cent. In several instances the recordings were unsatisfactory. In 2 patients louder systolic murmurs extending into diastole were observed. One patient proved to have patent ductus arteriosus at surgery.

Conclusion: More than half of the patients having suspected systolic functional murmur may avoid repeated visits which may induce anxiety and undesirable psychologic conditions in parents and older children. A few surgically correctable congenital lesions may be detected.

Pre- and Postoperative Cardiopulmonary Studies in High Pulmonary Flow Lesions without Pulmonary Hypertension

Lois T. Ellison, David P. Hall, and Robert G. Ellison, Augusta, Ga.

Cardiopulmonary physiology was studied before and after surgery in 13 patients with increased pulmonary blood flow. Five had atrial septal defects, 1 atrial septal defect plus anomalous pulmonary venous drainage, 1 atrial septal defect and pulmonary stenosis, 5 patent ductus arteriosus, and 1 femoral arteriovenous fistula. None had serious pulmonary hypertension and in the 12 patients in which a thoracotomy was done, lung biopsy obtained at surgery was interpreted as normal in all but 1 case.

Cardiac output, within normal limits before surgery, either remained the same or increased. The mean was 5.1 L. per minute, with an increase to 5.5 L. per minute. A significant left-to-right shunt was demonstrated in all cases with a mean pulmonary flow of 11.1 L. per minute with a mean left-to-right shunt of 6.3 L. per minute. Postoperative catheterizations revealed no shunts. The pulmonary artery pressure before operation was above normal or in the upper limits of normal (mean of 31/8) and decreased or was unchanged afterwards (mean of 27/7).

The alveolar-arterial oxygen difference, often above normal before surgery, while breathing room air and 30 per cent O₂, usually decreased after surgery. The value on 12 per cent O₂ was usually normal on both occasions. Venous admixture and physiologic dead space in the majority of patients remained within normal limits. However, the former tended to decrease and the latter to increase postoperatively. These changes apparently occur as a result of alteration in ventilation/perfusion ratio.

The possible clinical implications of this study have been considered.

Physiologic and Histologic Alterations Associated with the Experimental Production and Reversal of Pulmonary Hypertension

Robert G. Ellison, David P. Hall, Hessameddin Mobarhan, and Lois T. Ellison, Augusta, Ga.

Pulmonary function studies, with the simultaneous collection of expired air and arterial blood while breathing ambient air, 30 per cent O_2 , and 12 per cent O_2 , were performed on 30 normal dogs. Thereafter, staged bilateral subclavian-pulmonary artery anastomoses were done at approximately 6 week intervals. At operation, direct pulmonary artery pressure and lung biopsies were obtained. Pulmonary function studies were repeated at 2 month intervals. Cardiac catheterization was performed in conjunction with the above every 4-6 months. If, after 6-12 months, the pulmonary artery pressure had not increased to above 40 mm. Hg systolic, additional systemic-pulmonary artery shunts were created or the vascular bed reduced by lobectomy of "clipping" of the lower lobe pulmonary artery.

Alveolar-arterial oxygen difference in the controls was 12 mm. Hg while breathing room air, 10 mm. Hg with 12 per cent O_2 , and 37 mm. Hg with 30 per cent O_2 , with an average pulmonary artery pressure of 19/11 mm. Hg. After surgery in the animals with a pulmonary artery pressure of less than 40 mm. Hg systolic (average 32/13), the A-a difference was unchanged. However, in those with a pressure above 40 mm. (average 61/38) the A-a difference increased to 27 mm. with room air, 18 mm. with 12 per cent O_2 and 54 mm. with 30 per cent O_2 . These alterations, indicating both abnormal diffusion and venous admixture have been correlated with histologic findings.

A series of animals is at present being observed and data collected to determine the extent of reversibility of the above. The clinical implications of this study have been considered.

Hemodynamics of Experimental Total Pulmonary Valvectomy

Robert G. Ellison, Walter J. Brown, Jr., and William F. Hamilton, Augusta, Ga.

Pulmonary valvular insufficiency has been evaluated experimentally by complete excision of the pulmonary valves under direct vision, following which the dogs have been studied by repeated x-rays of the chest, electrocardiograms and cardiac catheterization. A total of 54 dogs were utilized in the study, 13 being evaluated from 2½

to 5½ years. Analysis of data and observations up to 14 months indicated that pulmonary insufficiency, resulting from complete pulmonary valvectomy, was tolerated remarkably well. Further evaluation demonstrated progressive cardiac enlargement, with reduction in resting cardiac outputs.

Early catheterization studies indicated a systolic pressure gradient across the pulmonary valve area. This gradient was confirmed by direct simultaneous recording of right ventricular and pulmonary artery pressures at thoracotomy. An average RV-PA systolic gradient of 6 mm. Hg was noted in 5 out of 10 cases. Surgically produced lesions which further increase the stroke volume (septal defects, patent ductus and A-V fistulae) showed RV-PA differences in systolic pressure in all 5 cases studied with an average of 8 mm. Hg after excision of the valves. In spite of markedly enlarged hearts and reduced resting cardiac outputs, there has been no evidence of heart failure except in 1 dog that had an associated peripheral A-V fistula. Recently some of the longest term animals have shown slight decrease in cardiomegaly. Data to show increased cardiac size, RV-PA pressure gradients and reduced cardiac outputs have been evaluated.

Plastic Reconstruction of a Flap Leaflet from the Aortic Wall for Correction of Aortic Insufficiency

Robert G. Ellison, David P. Hall, Hessameddin Mobarhan, Edwin L. Brackney, and William H. Moretz, Augusta, Ga.

In the past 3 years, experiments have been performed to study, under direct vision, the aortic valve, using the pump-oxygenator and cardiac arrest for the purpose of construction of a prosthetic valve leaflet. Flap valves constructed from teflon, pericardium and compressed Ivalon were abandoned in favor of 1 constructed from the aortic wall distal to the noncoronary sinus leaflet. This leaflet is turned inward so that it fits on the aortic valves without obstruction of coronary orifices. The aortic wall is patched with teflon. Flap shrinkage to two-thirds original size was demonstrated in 10 dogs in which flaps were created in the upper thoracic aorta.

In 22 experiments, the aortic valve was exposed for 15 minutes with 40 per cent incidence of resuscitation from cardiac arrest. In 10 experiments, plastic or pericardial flaps were placed, with no survivors. This was chiefly due to difficulties in resuscitation from cardiac arrest, accentuated by obstruction to coronary flow because of location or size of the flap. Five of 15 dogs survived after creation of aortic wall flaps. Most deaths were due to difficulties with cardiac resuscitation,

or bleeding from site of repair of the aortic wall. Flap leaflets have been evaluated by observation on a pulse duplicator and pressure measurements in the ascending aorta. The small size of the leaflet in relation to thickness of the aortic wall in the dog, hamper its function and this handicap may be overcome in larger aortas in humans.

Raynaud's Phenomenon as a Guide to Prognosis in Scleroderma

Richard G. Farmer, Ray W. Gifford, Jr., and Edgar A. Hines, Jr., Rochester, Minn.

The early appearance of Raynaud's phenomenon in the course of scleroderma has been regarded as a favorable prognostic sign. Since this has never been statistically verified, we reviewed all cases of systemic scleroderma (acrosclerosis and progressive diffuse scleroderma) seen at the Mayo Clinic from 1945 to 1952, inclusive. There were 271 patients; 199 (73.4 per cent) were women. The average age at time of diagnosis was 42.9 years.

Follow-up information for at least 5 years from time of diagnosis, or until death, was obtained on 236 patients (87 per cent). Of the 236 patients, 115 (48.7 per cent) had died, and the average age at death was 48.3 years. The average period between diagnosis and death was 41 months.

Raynaud's phenomenon was observed at some time during the course of the disease in 189 of the traced patients, of whom 93 (49.2 per cent) died during the follow-up period. This phenomenon was the first manifestation of scleroderma in 76 patients, of whom 36 (47.4 per cent) died; it was never present in 47 patients, of whom 22 (46.8 per cent) died.

Thus Raynaud's phenomenon had no bearing on prognosis in this series. Similarly, we could attach no prognostic significance to sex, sites of cutaneous involvement, or involvement of the esophagus, lungs or periodontal membrane. Cardiac and renal involvement, anemia and significant elevation of the erythrocyte sedimentation rate were all grave prognostic omens.

The results indicate that acrosclerosis and progressive diffuse scleroderma are artificial classifications with no clinical or prognostic value.

Mimetic Features of Rheumatic Fever Recurrences

Alvan R. Feinstein and Mario Spagnuolo, New York, N.Y.

Recurrent episodes of acute rheumatic fever have been analyzed in 161 patients who had 2 or more attacks, each of which fulfilled the modi-

fied Jones' diagnostic criteria. Valvular involvement in each attack was determined according to specific auscultatory features. These were a diastolic murmur at the base or left sternal border and/or a long systolic murmur, unequivocally loudest at the apex and transmitted to the axilla, with or without an apical mid-diastolic murmur.

Sixty-one patients, with a total of 129 attacks, had no valvular involvement with their first attack and none with subsequent attacks. They have remained free of heart disease. Ninety patients, with a total of 211 attacks, had evidence of valvular involvement with their very first attack. Their recurrences showed the same or new valvular involvement and, in many instances, there was additional cardiac damage. Only 10 patients did not conform to either of the above 2 patterns. They were found to have a diastolic murmur at a subsequent attack although none was noticed at their first attack. In 8 of these 10 patients, the murmur was discovered by a new physician or new hospital, suggesting that it might have been present at the first attack without being detected. Non-cardiac aspects of the attacks frequently showed repetitive features in the recurrent episodes in all groups of patients, especially in those with no valvulitis.

These results suggest that rheumatic fever attacks follow frequently mimetic patterns, and, in particular, that the rheumatic host has a fixed susceptibility to acquire or remain free of cardiac damage. Patients who do not get valvular involvement with their first attack seem to remain free of it despite recurrent attacks. Patients who develop heart disease, with doubtful exceptions, get evidence of it with their first attack. In this group, recurrences are particularly dangerous because they may make the cardiac damage recrudescence, or become worse.

In addition to their biologic implications, these data are pertinent to the clinical problem of selecting patients for continuous and indefinite antistreptococcal prophylaxis.

Effects of Physical Activity on Asymptomatic Patients with Potential or Rheumatic Heart Disease

Alvan R. Feinstein, Harry Taube, Ralph Cavalieri, Stanley G. Schultz, and Lawrence Kryle New York, N.Y.

The present study was made to determine the effects of physical and scholastic restrictions on the progression or development of heart disease in asymptomatic patients who have had rheumatic fever.

One hundred and ninety-eight patients with varying degrees of heart disease had been an

usually examined at the Irvington House After-Care Clinic for an average of 21 years following an attack of rheumatic fever. Each patient had had no rheumatic activity for at least 5 years and was essentially free of cardiac symptoms. A specific set of questions determined the restrictions these patients had observed with regard to: (1) school, (2) activities outside of school during the academic years (paraschool), (3) activities in home and life situations thereafter (postschool), and (4) any associated psychosocial effects. The present cardiac status and its changes over the years were independently determined and correlated.

School restrictions had been used in 129 patients; in 112 (87 per cent), the cardiac status was unchanged or better and in 17 (13 per cent) it was worse. In the 69 patients with no school restrictions, the cardiac status was the same or better in 64 (93 per cent) and worse in 5 (7 per cent). Significant psychological effects developed in 34 per cent of the 129 patients who had school restrictions and in 6 per cent of the 69 who had none. The cardiac status became worse in 13 per cent of 60 patients with paraschool restrictions and in 10 per cent of 138 who had none. Postschool restrictions were associated with a worsened cardiac status in 15 per cent of 40 patients who observed them and in 10 per cent of 158 patients who did not.

These results suggest that no useful purpose is served by many of the scholastic, athletic, vocational and other physical restrictions which are often imposed upon the asymptomatic post-rheumatic-fever patient, with or without overt heart disease. These restrictions do not seem to prevent or augment cardiac deterioration and they may create unpleasant psychosocial effects which negate any of the anticipated medical advantages.

Prevention of Therapeutically Induced Weight Gains in Hypertensive Patients

Harold S. Feldman, Livingston, N. J., and Raymond J. Gadek, Perth Amboy, N. J.

A series of 41 overweight hypertensive patients, ranging in age from 28 to 68 years, was placed on some form of rauwolfia for blood pressure reduction as required, and a low-salt, low-calorie diet. Adjunctively, levo-1-phenyl-2-aminopropane alginatate was employed to control the urge to eat usually associated with rauwolfia medication. The anorexigenic agent was administered t.i.d., before meals, in doses of 1 tablet (5 mg.) and, in a number of cases, at 8 p.m. as well. Observations during this present study indicate that this new appetite suppressant can safely be used in hy-

pertensives without CNS disturbance and it can be successfully used to combat night-time eating habits without causing insomnia. Weight reduction was obtained in 40 of the 41 cases under study, in spite of rauwolfia therapy which ordinarily tends to promote weight gain.

Prevalence of Various Streptococcal Types in Syracuse from 1950 to 1958

Harry A. Feldman, Syracuse, N.Y.

Little information is available on the prevalence of serologically different streptococci in 1 community. Since streptococcal immunity is type-specific and persistent, the local epidemiology of streptococcal pharyngitis and rheumatic fever may reflect the variety of streptococcal types that the population can experience.

Most diagnostic bacteriology in Syracuse is performed in 1 laboratory. Since 1950, all streptococcal cultures isolated there have been sent to us and approximately one-third have been grouped and typed. In the first 9 years, of 6,566 cultures, 73 per cent were group A, followed in decreasing frequency by G, C and B. Among 4,752 group A strains, 26 types were demonstrated but 47 per cent were nontypable. This problem became prominent in 1954 when 37 per cent were nontypable. The peak occurred in 1955 when 77 per cent were nontypable, gradually declining to 50 per cent in 1958. The commonest type has been 12, accounting for 15 per cent of all strains. Interestingly, 7 types and the nontypables account for 90 per cent of all strains. Thus, the opportunities for acquiring immunity to many streptococcal types in 9 years have been limited in Syracuse. If this is typical of other cities, it may explain the tendency for most rheumatic fever recurrences to occur within a few years after an attack. We found somewhat similar data in studies of cultures from Rochester, New York. The nontypable problem will be studied further. They cannot be dismissed as carrier types because many were isolated from cases of puerperal sepsis, including a fatal infection in a baby whose mother had this disease.

Microscopic Study of the Lungs in Tetralogy of Fallot, One to Twelve Years after the Creation of a Systemic-Pulmonary Anastomosis

Charlotte Ferencz, Cincinnati, Ohio, and Helen B. Taussig, Baltimore, Md.

A microscopic study of the lungs of 19 patients with congenital pulmonary stenosis, who died more than 1 year after operation, yielded important

information about the long-term prognosis of shunting operations.

Thrombotic lesions, present in the lungs of 75 per cent of unoperated patients, were absent in this late postoperative group. In patients who had a good anastomosis initially, but who lost the improvement with growth, there was a tendency toward the recurrence of thrombotic lesions. Patients who had a good clinical result and died of unrelated causes had normal lungs. Bacterial endarteritis damaged the pulmonary vascular bed by embolization. Chronic congestive cardiac failure in patients with a large anastomosis was associated with medial hypertrophy of muscular pulmonary arteries and intimal fibrosis, but this was not severe in any of the 3 patients in this series. Severe pulmonary hypertensive alterations were present in 3 patients who died 4-12½ years after operation. In all 3 instances, the anastomosis had been large initially and the changes in the lungs were similar to those observed in patients with malformations in which a high pulmonary blood flow represents the most significant physiologic alteration.

The findings of this study indicate that an anastomosis of moderate size is not only well tolerated for many years, but also has a beneficial effect on the pulmonary vascular bed by causing dissolution of thrombi, which often severely impair the vascular capacity of the lung in very cyanotic patients.

Preliminary Observations on the Pressor and Hemodynamic Properties of Angiotensin II in Man

Frank A. Finnerty, Jr.,† Gloria D. Massaro, Frederick J. Sigda, and John Tuckman, Washington, D.C.

The availability of angiotensin II (Ciba) prompted a comparison of its pressor and hemodynamic properties with those of noradrenalin. In 17 normotensive patients, the average effective doses of angiotensin II and noradrenalin were .028 µg. per Kg. per minute and 0.26 µg. per Kg. per minute, respectively. In these doses both agents produced an increase in arterial pressure from an average of 94 ± 11 to 131 ± 14 mm. Hg and a reduction in heart rate from an average of 78 ± 16 to 66 ± 17 beats per minute. Uremia (6 patients) decreased the pressor response to both agents.

An increase in arterial pressure from an average of 90 ± 11 to 128 ± 16 mm. Hg with angiotensin II was accompanied by a change in cardiac index (indicator dilution technic) in 10 patients from an average of $3.34 \pm .55$ to

$2.56 \pm .53$ L. per minute per M^2 during the infusion to $2.72 \pm .67$ L. per minute per M^2 following discontinuation of the infusion. There was no significant change in the plasma volume (I^{131}), red cell mass (Cr^{51}), hematocrit, sodium, potassium, chlorides, vital capacity, size of heart (x-ray), caliber of retinal arteries or the electrocardiogram.

Angiotensin II was found to be 6 to 10 times as potent as noradrenalin in 2 patients in shock. The arterial pressure and urinary output were maintained without symptoms for 30 hours and 8 hours, respectively. Three young patients without disease have received continuous intravenous infusions of angiotensin II over a 26 hour period. An increase in mean arterial pressure from an average of 86 ± 7 to 115 ± 10 mm. Hg has been maintained without symptoms, development of resistance, or decrease in urinary output.

Significance of Generalized and Lateral Retinal Sheen

Frank A. Finnerty, Jr.,† William D. Foote, Gloria D. Massaro, John Tuckman, and Joachim H. Buchholz, Washington, D.C.

Although studies from this clinic have reported the association of a wet glistening appearance of the entire retina with toxemia of pregnancy and acute glomerulonephritis, no objective data have been furnished regarding its specificity, etiology, or the manner in which this retinal sheen differs from the wet appearing retinas of normal young patients. Ophthalmoscopic examination was performed independently on 83 pregnant patients by 2 investigators without knowledge of the patients' history or physical findings. Included in this group were 30 patients with unequivocal signs of toxemia. Neither investigator found a generalized sheen in the 53 normal pregnant patients. Although the investigators did not agree on the findings in 5 toxemia patients, both investigators found a generalized retinal sheen in 23 patients.

In order to evaluate the retinas of young patients, ophthalmoscopic examination was performed independently on 294 patients of both sexes by 3 investigators. A generalized sheen was not found in any patient. Sheen of the lateral portion of the retina (using the optic disc as the dividing line) was noted in all 144 patients under 29 years of age, in 42 of the 56 patients between 30 and 40 years, and in 2 of the 62 patients over 40 years of age. Although chlorothiazide therapy promptly decreased the generalized retinal sheen of toxemia, it had no effect on lateral sheen.

It would seem (1) that generalized retinal sheen is an abnormal finding associated with

oxemia of pregnancy which probably represents retinal edema and (2) lateral sheen is normal in patients under 40 years of age.

Electrocardiographic Sequellae of Right Ventriculotomy in Patients with Ventricular Septal Defects: Abnormalities of Conduction and Evidence of Myocardial Injury

June M. Fisher, Ernest O. Theilen, Lewis January, and Johann L. Ehrenhaft, Iowa City, Iowa

Pre- and postoperative electrocardiograms were taken on 90 patients undergoing right ventriculotomy for repair of ventricular septal defects. Some electrocardiograms were obtained 1 to 2 years after operation to determine if certain changes observed early in the postoperative period disappeared later.

Before operation, an rR' type of QRS complex in right precordial leads, often referred to as incomplete right bundle-branch block, occurred in 19 per cent, and complete right bundle-branch block was found in 2 per cent. An additional 27 per cent showed evidence of right bundle-branch block after surgery. The changes of pre-existing incomplete right bundle-branch block regressed in some instances. T wave inversions in transitional leads and a decrease in T wave amplitudes, or occasionally inversions in left precordial leads, were the most consistent findings after closure of ventricular septal defects, occurring to some extent in the majority of patients. Evidence of actual myocardial infarction occurred in 2 patients.

Regression of the electrocardiographic changes of incomplete right bundle-branch block following closure of ventricular septal defects suggests the pattern is not necessarily due to an actual conduction disturbance, but instead supports the idea that the rR' deflections are a manifestation of right ventricular hypertrophy. Right bundle-branch block appearing after surgery probably represents an actual conduction disturbance due to surgery. The persistent T wave abnormalities in some cases suggest that myocardial damage may occur during ventriculotomy using extracorporeal perfusion, and that such damage is not confined to the area of the incision.

Transmural Ventricular Pressures in Experimental Cardiac Tamponade

Noble O. Fowler, Ralph Shabetai,* and John R. Braunstein, Cincinnati, Ohio

Brecher demonstrated that manual compression of the static viable dog left ventricle tended to produce negative intraventricular pressure upon

release of compression, pressure becoming more negative as intraventricular residual volume was decreased.

The observations reported here are designed to show that experimental cardiac tamponade, which may be expected to decrease diastolic ventricular volume, may also be associated with negative transmural ventricular diastolic pressure.

Transmural ventricular pressures during experimental cardiac tamponade were measured in 13 open-chest dogs. In 19 studies, negative diastolic left ventricular pressures of 1 to 6 mm. Hg were found during tamponade. In 11 studies, negative right ventricular diastolic pressures of 2 to 8.5 mm. Hg were observed during tamponade. In the left ventricle, negative transmural diastolic pressure developed when intrapericardial pressure was increased by a few millimeters of mercury and was sustained throughout diastole. In the right ventricle, negative transmural diastolic pressure occurred only with pericardial pressures above 10 mm. Hg, and was often limited to early diastole. Right and left ventricular systolic pressures declined when intrapericardial pressure was increased only a few millimeters of mercury.

At intrapericardial pressures of 10-20 mm. Hg, right ventricular systolic ejection often became greatly abbreviated and right ventricular pressure declined during left ventricular systolic pressure rise.

The results are consistent with the concept that impairment of ventricular filling during cardiac tamponade in the open-chest animal decreases ventricular diastolic volume, thus producing negative diastolic transmural pressure because of elastic recoil of the ventricles.

Hemodynamic Effects of Oligemic Anemia

Noble O. Fowler, Ralph Shabetai,* and John R. Braunstein, Cincinnati, Ohio

Previous studies of dogs receiving dextran infusions have suggested that the principal cause of the increased cardiac output and stroke volume was dilution anemia rather than hypervolemia. In the present study, 14 dogs under morphine-chloralose anesthesia were bled 20 ml. per Kg. (hypovolemia) and then made anemic by bleeding with dextran replacement in the amount of 60 ml. per Kg. (hypovolemic anemia).

Results: The mean hematocrit was 48.9 per cent in the control period and 16.2 per cent during hypovolemic anemia. The mean control blood volume (Cr⁵¹) was 1,410 ml. and was 1,192 ml. during hypovolemic anemia, $p < 0.001$. Control mean cardiac output was 1.935 L. per minute, falling to 1.207 L. per minute, $p < 0.001$, dur-

ing hypovolemia. During hypovolemic anemia, mean cardiac output rose to 2,807 L. per minute, significantly higher than in control or hypovolemic periods. Mean control stroke volume was 25 ml., falling to 11.2 ml., $p < 0.001$ during hypovolemia. During hypovolemic anemia, mean stroke volume increased to 18.7 ml., $p < 0.001$. Stroke volume increased in each animal during hypovolemic anemia as compared to the stroke volume during hypovolemia; however, right atrial transmural pressure did not increase in 10 of the 14 animals.

The results indicate that the cardiac output of dogs could be increased by anemia during hypovolemia, mean blood volume having been reduced by 15.5 per cent and hematocrit by 67 per cent. Stroke volume increased during hypovolemic anemia without increase in right atrial transmural pressure. No relation between right atrial transmural pressure and right ventricular stroke work was observed. Possible mechanisms of cardiac output response to anemia have been evaluated.

Pretracheal Left Heart Catheterization: Difficult Technique with Some Advantages

Samuel M. Fox, III, Bethesda, Md.

Both the transbronchial and posterior percutaneous methods of left heart catheterization have been found to have limitations. Suprasternal puncture, as proposed by Radner, provides access to the left atrium alone, since the fine needle employed may traverse the aorta and pulmonary artery. This technic was modified by the use of a double needle assembly, consisting of an inner no. 19 "exploring" needle extending 8 mm. beyond an outer no. 17-T needle, through which a catheter can later be passed. In 8 patients, attempts were made to pass this instrument posterior to the great vessels and anterior to the trachea. Satisfactory atrial pressures were obtained without complication in 5 patients. The left ventricle was catheterized in all 5, but it was impossible to stay across the valve in 2 patients with severe mitral insufficiency. In 1 of these, a knot formed in the catheter requiring thoracotomy. In 2 patients with severe pulmonary hypertension, the pulmonary arteries were repeatedly "explored" without sequelae, but the atrium could not be entered. In the eighth patient, with aortic regurgitation, the dilated aorta was unwittingly punctured by both needles. An asymptomatic mediastinal hematoma resulted.

The procedures were carried out with only skin anesthesia and the patients experienced little or no discomfort. The effects of exercise were studied

in 2 patients after the needle had been withdrawn over the indwelling catheter.

For physiologic studies, particularly of the effects of exercise and change in position, the method described has advantages. Difficulty and danger, however, appear to limit its routine use.

Morphology of the Delta Wave in the Wolff-Parkinson-White Syndrome

Theodore T. Fox, New York, N.Y.

There is still considerable controversy on the question of the mechanism of the WPW syndrome. Since the main criterion of the syndrome is the delta component of the QRS complex, a study of the morphology of this component in the electrocardiogram by pharmacophysiologic means was undertaken and a number of instructive illustrations was selected.

It appears that the structure of the delta wave depends largely on the amount of "vagus substance" available. Cholinergic influences increase the amplitude of this wave, while anticholinergic factors diminish its amplitude and on occasions lead to separation of this wave from what appears to be the normal QRS complex. This phenomenon leads to the assumption that the delta wave resides in the P-R area, which is the area most sensitive to vagus activity. The mere emergence of the delta wave is the result of an increase in the available vagus substance.

Thus, the delta wave, when emerged, is an electrocardiographic expression of an ectopic pre-ventricular focus capable of producing in association with the available sinus impulse a fusion beat.

This concept explains the usual short P-R interval and the bizarre QRS pattern of the WPW syndrome. It also accounts for the WPW beats without a preceding P wave, as well as the variations in the P-R interval observed not infrequently in cases demonstrating the WPW syndrome.

Acute Effects of Cigarette Smoking on the Digital Circulation in Patients with Peripheral Vascular Disease

Jack Freund and Clair Ward, Richmond, Va.

The present study is an extension of observations made on the normal male peripheral circulation after cigarette smoking. As in the prior studies, multitechnical procedures were utilized. These included skin temperature, digital plethysmography, radiosodium skin clearance, and A-V difference of oxygen saturation and lactic acid. In 14 patients, there were 26 studies performed. Arteriosclerosis obliterans was present in 12 pa-

tients and Raynaud's phenomenon and Buerger's disease in each of the remaining 2. All results were subjected to statistical analysis.

After smoking, there was no significant change from control values in the group of patients with any of the parameters of measurement. In previous studies, similarly performed in normal males, a significant reduction in peripheral skin temperature, radiosodium skin clearance, and venous oxygen saturation was observed after cigarette smoking. Although the results with plethysmography in the entire normal group showed a significant decrease, whereas no change was observed in patients with vascular disease, one area of similarity was the individual variability in both groups. The control values in all techniques were more homogeneous in normals than in those with vascular disease.

In summary, significant changes following smoking did not occur in patients with peripheral vascular disease when evaluated by skin temperature, radiosodium skin clearance, plethysmography and A-V difference of oxygen saturation and lactic acid. The variation in pathology in these patients and, in part, the decreased reactivity of tissue may account for the lack of significant change as compared to normals previously studied.

Effect of Exercise on the Level and Turnover of Plasma Nonesterified Fatty Acids

Samuel J. Friedberg,* William R. Harlan, David L. Trout, and E. Harvey Estes, Jr., Durham, N.C.

Plasma nonesterified fatty acid (NEFA) is a transport form of fat, the level of which is regulated largely by NEFA release from adipose stores. This study was designed to determine the effect of increased utilization by muscular exercise on both the plasma level and the turnover rate of NEFA.

Indwelling brachial arterial needles were introduced in each of 7 normal subjects. Control samples were drawn, immediately after which the subjects exercised vigorously on a stationary bicycle. Blood was drawn after 8 and 15 minutes of exercise, and 15 minutes after exercise was stopped. Plasma NEFA was determined by the Dole method modified to remove interfering lactic acid. The mean NEFA level was 0.87 mM per L. before exercise, fell to 0.64 mM per L. during exercise ($p < .01$) and rose to 1.02 mM per L. 15 minutes after exercise ($p < .01$).

To determine the nature of these changes, the difference in the disappearance of I.V. injected radiopalmitate tagged prepared NEFA was noted at rest and during exercise in 8 subjects. The mean half-life of tagged NEFA changed from

2.36 minutes at rest to 1.46 minutes during exercise ($p < .01$). The amount of NEFA entering and leaving the vascular compartment per minute (flux) was calculated, and was estimated to increase 25 to 45 per cent during exercise.

It is concluded that exercise not only lowers plasma NEFA concentration, but also increases the turnover rate and flux of plasma NEFA in man.

Evaluation of Heart Size in Children and Adolescents Who Have Had Rheumatic Fever

Julian Frieden, Alvan R. Feinstein, Jerome H. Shapiro, New York, N.Y., and Rodolfo DiMassa, Stratford, Conn.

The roentgenographic or electrocardiographic measurement of cardiac size in children and adolescents is difficult because criteria often differ from those used in adults. The present study evaluated the use of these methods in 105 children and adolescents, ages 6-20 years, who had had rheumatic fever. Of these, 70 had auscultatory evidence of residual heart disease.

Posteroanterior (PA), right anterior oblique (RAO), and left lateral (LL) chest x-rays with barium were "blindly" interpreted by 4 separate examiners and the results were also compared with independent fluoroscopic reports. With few exceptions, there was generally good agreement regarding ventricular size and very few "false positive" readings were made. In considering left atrial enlargement, there was frequent disagreement among examiners. The esophageal indentations were often difficult to interpret and showed many "false positive" results, as noted elsewhere in normal adults. In 35 patients with no heart disease, left atrial enlargement was diagnosed by at least 1 observer in 10 patients and by all observers in 4 patients. The "false positives" were somewhat fewer in LL than in RAO views; their incidence could be reduced by insisting that the retroatrial curvature involve both anterior and posterior esophageal walls.

The electrocardiograms failed to show left ventricular hypertrophy unless it was already radiologically apparent. Of 50 patients whose x-rays showed unequivocal left ventricle enlargement, 25 had normal electrocardiograms and none of the abnormal electrocardiograms showed left axis deviation beyond -30° , although this finding often occurs with congenital heart disease in this age group.

The results suggest that in the evaluation of heart size in young post-rheumatic fever patients: (1) the electrocardiogram is inferior to radiologic methods; (2) minor or occasionally definite indentations of the barium esophagram can occur

in normal patients and do not necessarily indicate left atrial enlargement; and (3) PA and LL chest films with barium are as accurate as fluoroscopy and offer permanent documentation with less radiation exposure.

Excretion of Epinephrine, Norepinephrine, and Other Hormones in Men Exhibiting a Behavior Pattern (A) Associated with Coronary Artery Disease

Meyer Friedman, Shirley M. St. George, Sanford O. Byers, and Ray H. Rosenman, San Francisco, Calif.

The urinary excretion of epinephrine (E), norepinephrine (NE), 17-ketosteroids, 17-hydroxycorticosteroids, and serotonin (5-hydroxy indole) was measured both during sleeping and working hours in 12 men (5 having coronary disease) exhibiting Behavior Pattern A (competitive drive, sense of time urgency, etc.) previously found associated with a high incidence of coronary disease. Similar measurements were done on men presenting a converse type of pattern B.

During sleep, excretion of all hormones was the same in both groups. However, the excretion of E increased 86 per cent (14.4 to 26.8 $\mu\text{g.}/1,000$ mg. of creatinine) during the day in group A and only 34 per cent (17.1 to 23.0) in group B. Excretion of NE increased 174 per cent (13.9 to 38 $\mu\text{g.}/1,000$ mg. of creatinine) during the day in group A, but only 74 per cent (13.2 to 21.6) in group B. Day excretion of steroids and serotonin was the same in both groups.

The observed excessive excretion of E and NE only during working hours in men exhibiting Behavior Pattern A (previously found associated with a high incidence of coronary disease) suggests: (1) possible involvement of these hormones in the pathogenesis of coronary disease; and (2) a mechanism whereby a particular Behavior Pattern A may influence the course of coronary disease.

Circulatory Responses to Hypervolemia and Their Modification by Ganglionic Blockade

Robert L. Frye and Eugene Braunwald, Bethesda, Md.

Although hemodynamic responses to acutely induced hypervolemia have been employed in evaluations of the applicability of Starling's law of the heart to intact man, interpretations of the results have been complicated by the hemodilution produced by infusion. Circulatory responses to whole blood transfusion were studied, both in the control state and during ganglionic blockade, in 7 subjects without heart disease. Each subject was phlebotomized 1,500 ml. during 1 week. On the

experimental day, this blood was reinfused in 90 minutes. Cardiac output and central blood volume, determined with the indicator-dilution method, and arterial and venous pressures were measured in duplicate immediately before and after transfusion. Phlebotomy was then repeated. Each study was repeated in otherwise identical fashion on another occasion, after ganglionic blockade had been induced and while it was maintained with a continuous infusion of Arfonad.

Transfusions in the control state resulted in average elevations of cardiac output of 0.50 ± 1.37 L. per minute and of left ventricular stroke work of 23.3 ± 33.8 Gm. M. per minute and a decline in central blood volume, which averaged 8 ± 131 ml. In each subject, the increase in each of these parameters resulting from transfusion during ganglionic blockade was substantially greater than in the control state and averaged 2.40 ± 0.61 L. per minute, 73.3 ± 25.7 Gm. M. and 348 ± 188 ml., respectively. Thus, in the presence of an intact autonomic nervous system, acute hypervolemia produced only minimal hemodynamic alterations. In contrast, during ganglionic blockade, hypervolemia evoked a cardiac response in man which more closely resembled that noted in the Starling heart-lung preparation when the venous return is increased.

Study of Thyroid: Digitalis Antagonism

Robert L. Frye and Eugene Braunwald, Bethesda, Md.

The ineffectiveness of digitalis in the treatment of heart failure and of atrial fibrillation occurring in hyperthyroid patients is well recognized. The present study was designed to assess quantitatively the relationship between digitalis and thyroid activity on a specific cardiac property, the refractory period of the atrioventricular node. The basal ventricular rate in patients with atrial fibrillation provided an index of the refractory period. Three euthyroid patients with atrial fibrillation were digitalized with digoxin and their basal ventricular rate determined during a control period. After 100-250 $\mu\text{g.}$ of triiodothyronine (T_3) was administered daily, the basal ventricular rate rose to an average of 132 per cent of the control value. In order to return the refractory period of the atrioventricular node to the control level, the daily dose of digoxin had to be increased to an average of 4 times the dose given during the control period and it was tolerated without digitalis intoxication.

In 1 undigitalized myxedematous patient with atrial fibrillation, the amount of acetylstryphanthidin required to slow the ventricular rate to 70 per minute was repeatedly determined after the

agal action of digitalis had been minimized by tropinization. The average dose of acetylstrophanthidin required in the hypothyroid state was 1.58 mg. and this rose to 1.50 mg. after the patient had been rendered euthyroid with T_3 . From these observations it is concluded that digitalis and thyroid exhibit antagonistic actions on the refractory period of the atrioventricular node. It is suggested that only the use of very large doses of digitalis may be therapeutically effective in the hydrocardiac patient.

Evaluation of Diuretic Activity of Four Thiazide Derivatives

Morton Fuchs, Sanford R. Mallin, and John H. Moyer, Philadelphia, Pa.

Three new thiazide derivatives, flumethiazide, hydrochlorothiazide and hydroflumethiazide have been evaluated by us and compared clinically and pharmacologically with chlorothiazide. Bio-assay studies have been used to determine dose response curves and comparative potency estimations. Statistical analysis of sodium and chloride excretion shows an effective dose range of 250 mg. to 2,000 mg. for chlorothiazide and flumethiazide, 25 mg. to 200 mg. for hydrochlorothiazide, and 25 mg. to 400 mg. for hydroflumethiazide. The natriuretic potency of these drugs at their optimal dose is essentially the same. Chloruresis is less than natriuresis with chlorothiazide and flumethiazide but exceeds sodium excretion following hydrochlorothiazide and hydroflumethiazide administration. Potassium excretion, however, does not rise proportionately with larger doses, particularly with flumethiazide and hydroflumethiazide. Potency estimations and dose response curves were also obtained by measuring the 48 hour weight loss of edematous patients at varying doses of the drugs. These correlated well with sodium loss in the bio-assay studies. Renal function studies showed no significant change in glomerular filtration rate or renal plasma flow. Chronic drug administration to edematous patients showed continuing effectiveness of these agents, whose diuretic activity is dependent on inhibition of renal tubular reabsorption.

Effect of Sublingual Heparin on Recurrence of Myocardial Infarction

Harvey L. Fuller,† Baltimore, Md.

The essential role of heparin in lipid metabolism and its postulated relationship to atherogenesis have previously been reported, as has the ability of twice-weekly injections of heparin to reduce the incidence of recurrent myocardial infarction.

In acute experiments, sublingual heparin has

been found to clarify postprandial lipemic serum, although not as rapidly as parenteral heparin. Clarification apparently results from the physical breakdown of chylomicrons into smaller and more readily utilized particles, rather than from chemical alterations in the lipid fractions. Thus, no immediate effect on serum cholesterol, phospholipids or total lipids is observed, nor is coagulation time prolonged. Administration of heparin rectally, by swallowing, and by duodenal intubation does not clarify lipemic serum nor alter coagulation time.

A series of 130 postcoronary patients has been treated with sublingual heparin 3 times daily after meals for periods up to 4 years. An equivalent number of matched controls, each with at least 1 previous, proved myocardial infarction, received conventional treatment but no heparin in any form. During the period of observation, a marked, statistically significant reduction occurred in the incidence of recurrent infarction in the treated group as compared to the control group.

Sublingual heparin appears to be a valuable adjunct to the long-term management of the postcoronary patient. Since it requires no clotting determinations, it has obvious advantages over the regular use of oral anticoagulants and is preferable to the sporadic use of parenteral heparin. Further study in other clinical manifestations of atherosclerosis should be rewarding.

†Deceased.

Ballistocardiography in the Newborn: Experience with a New Type of Instrument

Walter J. Gamble, Philadelphia, Pa.

Our ultra-low-frequency undamped ballistocardiographic bed with 2 accelerometers attached weighs 240 Gm., light enough for all but the lightest 3 per cent of newborns. Infants placed on the bed are induced to sleep without drugs. Head-foot and lateral acceleration ballistocardiograms and electrocardiogram lead I are recorded. Fifty clinically normal infants were tested between 1½ hour and 5 days of age, often repeatedly, and 25 infants between 1 week and 6 months of age were also tested.

The average I-J amplitudes showed a marked decrease with aging during the first 20 extrauterine hours, which might be due either to a reduction in the patent ductus blood flow, or increasing peripheral resistance, or both.

Considerable rise in the I-J amplitude was found immediately after the initial feeding given 20 hours after birth. During the next 4 days there was no significant correlation between amplitude and age, or between amplitude and time since feeding.

Very early in life, notching of the H-I, I-J, and J-K segments was prominent. This decreased during the first 5 days of life and usually disappeared by 2 weeks of age. These notches probably signify asynchronous ejection from the right and left ventricles.

It is probable that the changes in the ballistocardiograms in the neonatal period reflect the changes in the dynamics of the circulation occurring during the transformation from fetal to adult form. Our evidence indicates that this transformation is frequently incomplete on the fifth day, but is usually complete by 2 weeks of age.

Congenital Coronary Arteriovenous Fistula: Clinical, Angiocardiographic, and Physiologic Findings on Five Patients

Benjamin M. Gasul, Rene A. Arcilla, Joshua Lynfield, J. Pedro Bicoff, and Lawrence L. Luan, Chicago, Ill.

Five cases of proven coronary arteriovenous fistula were studied. Phonocardiograms, angiocardiograms including retrograde aortograms, and cardiac catheterization were done before and after surgery. Three cases were correctly diagnosed preoperatively. Four were successfully operated on and the surgical aspects have been previously reported. A 3 week old infant is as yet unoperated. This paper deals with our heretofore unpublished phonocardiographic, angiocardiographic (venous, selective, and retrograde aortogram), and hemodynamic findings in this entity.

There were 3 males and 2 females and the ages varied between 3 weeks and 19 years. In 1 case the left coronary artery opened into the right ventricular outflow tract and the clinical findings were indistinguishable from those of a patent ductus. In the others the right coronary artery communicated with the inflow or apical region of the right ventricle. The characteristic finding was a loud, superficial, continuous murmur over the lower precordium. The x-ray findings were not specific. The electrocardiogram was normal in 1 and showed mild to moderate left ventricular hypertrophy with incomplete right bundle-branch block in the others. Cardiac catheterization revealed a left-to-right shunt at the ventricular level ranging from 0.7 L. per minute per M^2 to 6.6 L. per minute per M^2 and normal or slightly elevated pulmonary artery pressures. In 2 cases, the venous angiocardiogram clearly outlined the dilated and tortuous coronary artery. The fistula was best outlined however, by retrograde aortography. The ascending aorta was dilated in all cases. The postoperative hemodynamic studies were normal.

The cardiac catheterization findings are not specific since they merely indicate the level of the shunt. Peripheral venous or selective angiocardiog-

raphy and preferably, retrograde aortography, however, are diagnostic.

Study of a Large Spectrum of Adrenocortical Hormones in Urines of Normal Subjects and Hypertensive Patients

Jacques Genest, Erich Koiw, Wojciech Nowaczynski, and Thomas Sandor, Montreal, Canada

The following adrenocortical hormones were simultaneously studied in urines obtained from normal subjects and hypertensive patients: aldosterone, cortisone, tetrahydrocortisone, hydrocortisone, tetrahydro-hydrocortisone, tetrahydro-17-hydroxy, 11-desoxycorticosterone, etiocholanolone and pregnanetriol. Their determinations were done after isolation according to procedures described elsewhere. Results obtained with 165 individual aldosterone determinations in 96 normal subjects and hypertensive patients confirm previous findings of a statistically significant increase in mean aldosterone excretion ($p < 0.01$) in patients with essential, renal and malignant hypertension as compared to normal subjects. Daily determinations of urinary aldosterone showed excessive fluctuation in hypertensive patients, but not in normal subjects studied under ordinary working conditions. Mean urinary pregnanetriol excretion (Bongiovanni's procedure) is statistically significantly decreased in groups of patients with essential, renal and malignant hypertension as compared to that of normal subjects ($p < 0.01$). From these findings, we have derived a ratio of urinary pregnanetriol/aldosterone, the mean of which is highly significantly decreased in all 3 groups of hypertensive patients as compared to normal subjects ($p < 0.01$). This ratio is, we believe, highly suggestive of hypertensive disease in the absence of clearly defined clinical endocrine disorders. No significant difference was found in the other hormones studied: cortisone, hydrocortisone and their tetrahydro derivatives, the tetrahydro derivative of compound "S" and etiocholanolone. On the basis of these and other electrolyte studies, a new concept tying together adrenal cortex, kidneys, renin-angiotensin system and sodium has been formulated.

Surgical Treatment of Valvular Pulmonary Stenosis Using Extracorporeal Circulation

F. Gerbode, G. A. Harkins, and J. K. Ross, San Francisco, Calif.

Although blind procedures have been advocated for the relief of valvular pulmonary stenosis by many operators, the open operation has gained the most support in recent years. At the present time, the strongest advocates use hypothermia as

an adjunct for this operation. During the past 2 years, this unit has employed extracorporeal circulation for all patients who had a diagnosis of valvular or infundibular pulmonary stenosis.

A substantial experience has been gained in the management of these patients. There have been 4 instances of unsuspected interventricular septal defect in the series, and a surprisingly high incidence of infundibular pulmonary stenosis, both of the work hypertrophy type and perhaps also of the congenital type. In some instances, at least, although the valvular stenosis has been relieved, after a period of waiting the work hypertrophy stenosis has not completely disappeared and has required further open operation.

Elective Hypothermia During Extracorporeal Circulation with a New Heat-Exchanging Filming Oxygenator: Indications and Results

F. Gerbode, J. J. Osborn, L. M. Bramson, G. A. Harkins, and J. K. Ross, San Francisco, Calif.

Approximately 100 patients have undergone cardiac surgery, using a pump-oxygenator with elective hypothermia induced by lowering the temperature of the perfusing blood.

A rotating filming oxygenator has been designed (by Osborn and Bramson) which is also inherently a heat exchanger and contains a very low priming volume in relation to oxygenating surface. The internal surface of this apparatus is factory processed and inserted as a pyrogen-free, preassembled integral unit. A large part of the oxygenating surface is available for heat exchange, thus the apparatus provides rapid changes of blood temperature and precise control of temperature, as required, without a separate heat exchanger.

As compared with a previous series of 100 patients who were maintained normothermic during perfusion for cardiac surgery, the patients electively cooled had smoother postoperative courses, with less postoperative fever, and fewer complications. This may have been related to the fact that coronary flow appeared to be reduced by the hypothermia, and the patient's oxygen requirement was lower so that any periods of reduced atrial flow may have been better tolerated.

Simple Colorimetric Urinary Analysis for the Diagnosis of Pheochromocytoma

Stanley E. Gitlow, Leonard Ornstein, Sarah Khassis, and Milton Mendlowitz, New York, N.Y.

A chromatographic analysis of urinary vanillyl-mandelic acid (VMA), a catecholamine metabolite, has been recently demonstrated to be diagnostic of pheochromocytoma. This test has been modified to provide a simple and rapid colorimetric screening procedure.

The patient is directed to abstain from fruits, certain beverages, and drugs for 24 hours, after which a fasting morning urine specimen is collected. An aliquot equivalent to 0.5 mg. creatinine is hydrolyzed at pH 2 and 100 C. for 15 minutes. The urine is extracted with ethyl acetate, blown to dryness, and redissolved in 2 ml. H₂O. One milliliter 5 per cent K₂CO₃ is added, the solution shaken, and 1 milliliter of diluted diazotized p-nitroaniline is added with constant mixing. N-amyl alcohol-ethanolamine (20:1) is added, the mixture shaken vigorously, centrifuged, and the organic solvent separated for reading on a Beckman DU Spectrophotometer at 450 mμ. and 550 mμ. (vs. H₂O blank). The ratio of these 2 readings

$$R = \frac{\text{density at 450}}{\text{density at 550}}$$

exceeded 1.25 in all of the 15 normal urine specimens and in the 15 specimens from patients with primary hypertension (range 1.25 to 2.20; mean 1.69). Urine from 15 patients with pheochromocytomata revealed R values of 0.67 to 0.98 (mean 0.79). Pheochromocytoma has been shown to be associated with at least 3.75 μg. VMA/0.5 mg. urinary creatinine (range 3.75 to 20). R values for normal urine, to which 3.0 and 5.0 μg. VMA had been added, averaged 1.16 and 1.01, respectively. Since no overlapping of R values has been observed between patients with primary hypertension and those with pheochromocytomata, hypertensive subjects can be quickly and accurately screened by means of this test for the presence of pheochromocytoma.

Clinical and Experimental Study of Bilateral Internal Mammary Artery Ligation (Bimal) for the Relief of Angina Pectoris

Robert P. Glover, J. Roderick Kitchell, Julio C. Davila, and Howard T. Barkley, Jr., Philadelphia, Pa.

A variety of surgical methods have been employed over the years in an attempt to increase myocardial blood supply and distribution. The most recent of these, ligation of the internal mammary arteries bilaterally, originated in Italy and was introduced into this country by the authors. This report summarizes the experimental evaluation of this procedure and details the clinical results obtained in 219 patients suffering from post coronary occlusion angina pectoris followed from 1 to 2½ years.

Two hundred and forty-four experiments on animals have reaffirmed the presence of anastomotic collaterals between the internal mammary arterial system and the coronary arterial system, but no actual increase in myocardial blood flow has been demonstrated following the operation.

Clinically, 46 per cent of this series of patients have shown moderate to marked improvement and 63 per cent have shown slight to marked relief. Lacking evidence to the contrary, we must assume that the benefit observed consists solely in the relief of anginal pain by mechanisms (psychosomatic, neurogenic, etc.) as yet unknown.

Internal Mammary Coronary Artery Anastomoses

Robert H. Goetz, Michael Rohman, Jordan D. Haller, and Stephan Rosenak, New York, N.Y.

Surgical attempts to improve coronary artery circulation in the presence of thrombosis or arteriosclerosis have met with modest success. Various methods have been employed to increase myocardial blood supply with the underlying principle of either encouraging capillary anastomoses, or directly restoring the blood flow in the diseased vessels.

Autopsy studies have demonstrated that a significant number of patients with coronary artery obliteration have a segmental obstruction in close proximity to the origin of the main coronary arteries.

Bypass of the occlusion by the creation of a systemic coronary artery anastomosis appears, therefore, a rational method of improving the blood flow to the distal myocardium.

The first attempts utilizing direct suture techniques between the internal mammary and left anterior descending artery were uniformly unsuccessful. Therefore, a nonsuture technic was employed. A siliconized tantalum ring with a lumen approximating that of the coronary artery (2 to 3 mm.) is used to cuff the transected end of the mobilized mammary artery. The cuffed vessel is then inserted through a longitudinal incision into the coronary artery and tied in place. The method has permitted successful anastomoses in less than 2 minutes and animals with both the left anterior descending and circumflex branches on systemic circulation are alive up to 1 year. The results of this procedure have been encouraging.

Clinical and Physiologic Findings Following Open Surgical Treatment for Aortic Stenosis

Harry Goldberg, Joseph Uricchio, Janet Dickens, Lamberto Bentivoglio, and William Likoff, Philadelphia, Pa.

Reconstruction of the aortic valve by open heart surgery has been performed in 30 patients. There were 5 (16 per cent) operative deaths due to ventricular fibrillation, cardiac arrest or gastrointestinal bleeding.

Follow-up studies, 6 months to 1 year, reveal all but 1 patient improved symptomatically.

Striking changes were recorded in the postoperative phonocardiograms. The systolic ejection murmur was reduced in intensity and occasionally changed in configuration, while the aortic second heart sound became more prominent. Dynamic aortic regurgitation was not produced. No remarkable changes in the electrocardiogram or chest roentgenogram were noted.

Physiologically, relief of obstruction was demonstrated by elimination or marked reduction in the aortic systolic pressure gradient, decrease in both systolic and diastolic left ventricular pressures and increase in aortic valve flow and calculated areas. Pulmonary hypertension decreased in those patients in which it was present preoperatively.

These results are contrasted with those obtained in over 200 patients with aortic stenosis operated upon by closed techniques. It is concluded that open heart surgery, with valvular reconstruction, permits more satisfactory relief of obstruction.

Preoperative Roentgenographic Evaluation of the Proximal Aorta and its Branches

Edward I. Goldsmith and Nathaniel Finby, New York, N.Y.

Certain diseases of the proximal aorta and coronary arteries can now be treated surgically. Safe and reliable preoperative visualization of these structures is desirable. A cooperative experiment program in the departments of surgery and radiology was undertaken to develop a satisfactory method of selective retrograde aortography and coronary arteriography. This was accomplished after exhaustive animal experiments had been performed to evaluate various techniques, equipment, and contrast media.

The following principles were evolved: Optimal precaution for patient safety includes the participation of an anesthesiologist and a cardiovascular surgeon. Retrograde placement of an appropriate catheter is best performed through a femoral arteriotomy with subsequent precise repair of the vessel. The tip of the catheter must be accurately placed without undue trauma or excessive irradiation. The contrast medium must be safe and of high radiographic density. Precise studies depend upon an optimal relationship between the following factors: dose of the contrast medium, cardiac rate, speed of injection, speed and frequency of radiographic exposures.

Close cooperation among experienced personnel will assure a high degree of diagnostic dependability. The technic has been successfully applied to the diagnosis of coronary artery disease, aortic valvular disease, and various left-to-right shunts at the origin of the aorta.

Heart Sounds Recorded Along the Transbronchial Needle and from the Heart Exposed During Surgery

Alvin J. Gordon, Edward Henry, Paul A. Kirschner, Gabriel Jenkins, and Howard L. Moscovitz, New York, N.Y.

Two new techniques of phonocardiography are here reported:

1. In the course of left heart catheterization by the transbronchial route, vibrations were felt and recorded along the transbronchial needle by a contact-type microphone designed for amplification of stringed instruments (Brush Vibra-mike). In mitral stenosis, the first and second sounds were sometimes visible, and in aortic stenosis the ejection murmur could be recorded. Of special interest, however, were the findings in mitral insufficiency, in which the systolic murmur was clearly visible but was of greatest intensity when the tip of the catheter, passing through the needle, lay in the left ventricle. It appeared that the catheter in this location acted as a resonating string. This phenomenon was noted in 1 patient without a systolic murmur who was thought to have pure mitral stenosis. At operation, a regurgitant jet was found.

2. Preliminary experiences have also established the value of the recording of sounds and murmurs from the heart exposed during surgery. The Altec 21MA condenser microphone may be sterilized by dry heat and placed directly on the epicardium. Sounds are simultaneously amplified on a loud speaker, recorded on tape and photographed on an oscillograph, together with pressure pulses obtained by needle puncture. Phonocardiograms thus obtained closely resemble those recorded from the chest wall, but are more sharply localized to the chambers of origin.

Glycogen, Lactic Acid and High-Energy Phosphate Levels During Hypothermic Arrest of the Human Heart

Vincent L. Gott, David M. Long, John A. Johnson, Marilyn M. Bartlett, and C. Walton Lillehei, Minneapolis, Minn.

At the University of Minnesota Hospitals, selective hypothermic arrest has been used for the past year in preference to potassium citrate arrest for cases undergoing direct vision cardiac surgery. Utilizing this newer technique, the myocardium is perfused with cold blood until the temperature is reduced to 17 C., or below. At this temperature, the heart is in complete standstill and the coronary perfusion may be stopped to provide a dry field for the surgeon, or the coronary perfusion may be continued at a fraction of the normal flow while the intracardiac procedure is performed.

In most cases in this study, the heart was open and arrested for 45-60 minutes and the coronary perfusion was used intermittently for about two-thirds of that time period.

In 10 cases in which hypothermic arrest was utilized, biopsies were taken of the right ventricular myocardium at the beginning and end of the arrest period. Because no 2 cases were similar with regard to duration of arrest or intermittency of myocardial perfusion, mean values could not be determined. The results in all cases were similar enough, however, to allow certain conclusions to be drawn. The glycogen level usually fell only slightly from an initial level of 800 mg. per 100 Gm. The lactic acid usually rose 40 mg. per cent from an initial level of 20 mg. per cent. The ATP decreased only slightly from an initial level of 4 mM per Kg. and the ADP rose only slightly from an initial level of 0.8 mM per Kg. Phosphocreatine, which is a small storehouse of readily available high energy phosphate, usually fell from 3 mM to 1 mM per Kg.

In a similar study of cases in which potassium citrate arrest was used for a relatively short time (8-20 min.) the glycogen and ATP fell significantly (frequently to one-half the initial value), the lactic acid rose to levels near 100 mg. per cent, or over, and the phosphocreatine fell to zero.

The technique of selective hypothermic arrest seems to offer several obvious advantages over potassium citrate arrest, which become particularly important in the patients with low myocardial reserve preoperatively. It provides complete cardiac arrest yet obviates the deleterious effects of hypoxia by allowing for intermittent coronary perfusion. In addition, by lowering the temperature of the myocardium from 37 to 17 C, the energy requirements are reduced to approximately 25 per cent of normal (physiologic Q_{10} being 2) thus greatly lengthening the duration of safe arrest.

Gallop Rhythm of the Heart

Joseph Grayzel, New York, N.Y.

Gallop rhythm is defined as a mechanical event associated with a relatively rapid rate of ventricular filling and characterized by a localized ventricular thrust and a low-frequency sound. Since these phenomena occur during early and late diastole, 2 fundamental types of gallop exist: rapid-filling (or ventricular) gallop and atrial gallop.

Seventeen patients with gallop rhythm were studied. The fundamental frequencies of the gallop sound were 25-50 c.p.s. Rapid-filling gallop of the left heart occurred 0.15 second after the beginning of the second heart sound except in

mitral insufficiency where this interval was 0.10 second. Left atrial gallop occurred 0.14 second after the onset of the P wave.

The cases studied indicate that atrial gallop signifies ventricular hypertrophy and is not related to heart failure. Rapid-filling gallop accompanied diastolic overload, either secondary to heart failure or valvular insufficiency.

When both types of gallop are present in each cardiac cycle sufficient increase in heart rate will superimpose the 2 to produce summation gallop. When a rapid-filling gallop is superimposed upon a silent phase of atrial contraction it may be augmented mechanically and acoustically, and is called augmented ventricular gallop. Similarly, an atrial gallop superimposed upon a silent period of rapid ventricular filling may be intensified and is called augmented atrial gallop.

Two equations have been derived which express the summation cycle length or the summation rate, respectively, as a function of the P-R interval. A graphic representation of this relation has been constructed. The equations and graph are valid for the summation and augmented gallops. The equation for the summation cycle length is also valid when summation is produced by a premature atrial contraction.

Rhabdomyoma of the Heart: Preoperative Diagnosis and Open Operation

Edward W. Green and Rodman E. Taber, Detroit, Mich.

Accurate diagnosis of primary intramyocardial tumors during life has been rare, especially with the production of hemodynamic changes necessitating surgical interference. Previous experience with a 1 month old infant showing, clinically and physiologically, a mild pulmonic stenosis aroused interest in this condition when later it was found that rhabdomyosarcoma of the ventricular septum was present. More recently, a 7 year old boy presenting clinically as pulmonic stenosis was correctly diagnosed preoperatively as "benign" tumor of the ventricular septum. Open operation was performed, utilizing a pump oxygenator; a 3 cm. noncontractile muscular appearing tumor of the ventricular septum was found obstructing the right ventricular outflow tract. Extensive resection of the obstructing tissue was done after frozen sections were found compatible with benign rhabdomyoma. Nine months after operation, the patient is now well and without clinical evidence of any recurrent right ventricular obstruction.

The atypical features of the electrocardiogram and catheterization which led to this suspicion will be amplified. An angiocinemographic study,

illustrating the tumor, has been made, as well as photographs of the operative field and pathologic studies.

Clinical Use of Retrograde Left Ventricular Catheterization in Congenital Heart Disease

Edward W. Green, Robert F. Ziegler, and Doris Kavanagh-Gray, Detroit, Mich.

Recent advances in direct vision surgery on left-sided congenital heart lesions, such as aortic stenosis, have increased the need for a simple, safe, routine method of obtaining left ventricular and aortic pressure relationships. Retrograde left ventricular catheterization from a peripheral artery would appear to circumvent many of the objections to left heart needle puncture techniques, especially in small infants. The present study is an evaluation of this procedure in 100 patients with forms of congenital heart disease where left ventricular pressure measurements or angiocardigrams were felt to be desirable, and the left side of the heart could not be entered via the foramen ovale during right heart catheterization. The age range was from 6 weeks to 28 years.

The left ventricle was successfully entered in 88 per cent. Marked dilatation of the aorta, or difficulty entering the ascending arch, were the most common reasons for failure. The danger of coronary artery blockage by the catheter can be eliminated by continuous pressure monitoring and good fluoroscopic control. There has been no complication in any case, and good functional repair of the brachial artery was achieved routinely. The routine acceptability of this procedure is indicated by the fact that 47 consecutive cases were successfully done in the latter part of the series, with only 1 failure.

Retrograde Brachial Aortic Cinefluorography: A Valuable Technic in the Diagnosis of Patent Ductus Arteriosus and Coarctation of the Aorta in Infancy

Robert S. Green, Erna L. Borousch, Fernando L. Mendez, Robert D. Mansfield, Joseph M. Schuster, Jr., Paul G. Geiss, and Muzaffer Aytur, Cincinnati, Ohio

A retrograde brachial aortic cinefluorogram is obtained as the first procedure of choice in all acyanotic infants with an enlarging heart and a systolic murmur. Frequently, these infants are in congestive failure when first observed. Radioopaque dye is injected in the brachial artery in a retrograde direction with the patients in the LOA position. Three hundred full chest motion picture x-ray films are obtained over a 10 second period during this procedure. Multiple exposures are

necessary because of marked tachycardia in these infants. Diagnostic frames are limited, usually to 3 second (10 frames), for each of 3 or 4 heart cycles. These films are reviewed with a specially constructed 35 mm. analyzer that permits forward or reverse single frame or motion analysis of from 1 to 24 frames per second. Individual frames show excellent detail of the aorta and larger arteries; the dynamics of arterial flow are demonstrated with motion studies.

This paper details our results in 4 infants. Films suggestive of a patent ductus were obtained in 1 infant, 17 days old. An insignificant ductus was found at operation. Autopsy demonstrated multiple other congenital defects as the cause of failure. An uncomplicated patent ductus arteriosus that was subsequently corrected by surgery was demonstrated in 2 infants, age 4 and 6 months, respectively. A 4 month infant, with a normal aortic cinefluorogram, was shown to have an interventricular septal defect by a subsequent right heart catheterization. There have been no complications during this procedure.

Expired Air Resuscitation During Cardiac Emergencies

David G. Greene and James O. Elam, Buffalo, N.Y.

With the increased interest in the treatment, outside the operating room, of cardiac emergencies, such as ventricular standstill and ventricular fibrillation, the problem of pulmonary ventilation under these conditions becomes important. It has been repeatedly emphasized that good oxygenation is essential for the re-establishment of normal rhythm. Any physician, or trained aide, without any equipment, may provide adequate pulmonary ventilation during an emergency thoracotomy simply by blowing his own breath into the nose or mouth of the victim. We have provided excellent tidal volumes by this method in diverse cardiac emergencies. During cardiac arrest in a post-thoracotomy patient, excellent lung ventilation was easily provided while a surgeon reopened the wound and provided cardiac massage. The success of the maneuver was easily seen through the thoracotomy wound, as the lungs filled and emptied rhythmically.

This form of artificial respiration may stimulate the heart beat as well as provide ventilation. Following a cardiac arrest during cardiac catheterization, prompt institution of ventilation by this method not only gave good gas exchange but it was followed by the return of P waves and then of normal rhythm, all before there was time to open the chest for cardiac massage. Pulmonary edema, with severely diminished pulmonary compliance and pronounced hypoxia, responded

better, temporarily, to expired air resuscitation than to intermittent positive pressure with oxygen. A simple pocket mask carried on the person fits over the nose and mouth of the victim and allows avoidance of direct lip contact.

Clinical and Cardiodynamic Effects of Adrenocortical Steroids in Congestive Heart Failure

Murray A. Greene, Arthur Gordon, and Adolph J. Boltax, Bronx, N.Y.

This study is concerned with the effects of adrenocorticoids in patients with congestive heart failure and with mechanisms in edema formation.

Nine adults with heart failure were studied during steady clinical states (5 to 7 days), during 13 to 16 days of prednisone (6 patients) or triamcinolone (3 patients) administration, and in some subjects following steroid withdrawal. Daily determinations of fluid balances were made. Standard right heart catheterizations and measurements of blood volumes were performed before and at the termination of therapy.

Three types of responses to steroids occurred:

1. In 5 patients accentuation of subjective and objective manifestations of heart failure and increased fluid retention occurred. Four developed precarious clinical conditions during steroid therapy, requiring mercurial diuretics, but with poor results. In general, cardiodynamic status at the termination of steroid therapy correlated well with clinical status.
2. In 3 patients no change in clinical status occurred. Some depression in urinary Na and Cl excretions were noted during therapy. Cardiodynamics were unaltered except for an unexplained decrease in right ventricular end-diastolic pressure in 1 patient.
3. In 1 patient improvement occurred in clinical state and cardiodynamics, despite positive fluid balance. This was the only subject with primary lung disease (emphysema) and cor pulmonale.

These studies suggest that corticosteroids are generally detrimental in uncomplicated congestive heart failure. Greater deterioration appeared to occur in subjects (group 1) having more severe degrees of decompensation, suggesting that exogenous fluid-retaining influences were added to endogenous fluid-retaining forces, resulting in further accumulation in a circulatory system already burdened by hypervolemia.

Cardiovascular Dynamics of Vasovagal Reactions in Man

Murray A. Greene, Adolph J. Boltax, and Robert J. Ulberg, Bronx, N.Y.

Knowledge of circulatory changes which take place during the commonly occurring "vasovagal

reaction" in man is incomplete. The dynamics of vasovagal reactions which occurred in 2 patients during right heart catheterization have been studied. Most cardiac output determinations were made using the Stewart-Hamilton principle.

Both subjects initially had systemic hypertension, minimal in subject A, severe in subject B, with corresponding increases in peripheral resistances. Subject B had considerably decreased blood flow, moderately elevated pulmonary artery and right ventricular end-diastolic pressures, and elevated central blood volume. These parameters were normal in subject A.

The characteristic features of the reactions were appreciable declines in cardiac outputs coincident with decreased systemic arterial systolic, diastolic, and pulse pressures, decreased heart rates, and slight increases in calculated peripheral resistances. Stroke volumes were moderately reduced. No changes in right heart pressures occurred in subject A. In subject B, pulmonary artery and right ventricular end-diastolic pressures declined to normal and central blood volume decreased moderately. The return of heart rate to control values, following intravenous atropine in subject A and spontaneously in subject B, had no significant effects on the other physiologic parameters.

This evidence re-emphasizes: (1) the importance of venomotor tone and venous return in regulating cardiac output which, in turn, affects blood pressure and, inversely, calculated peripheral resistance; (2) the relative unimportance of bradycardia; (3) the ineffectiveness of atropine in restoring cardiodynamics; and (4) the increased venomotor tone of heart failure. The failure of peripheral resistance to compensate for diminished blood flow suggests inhibition of arteriolar tone.

Neglected Cause of Variability in the Duration of Systole in Patients with Atrial Fibrillation

Geraint T. Griffith,* Buffalo, N.Y.

In 42 patients with atrial fibrillation, the duration of mechanical systole of the left ventricle ($q-A_2$) was plotted for each beat against the reciprocal of the previous cycle length (rate). A linear relationship was observed which could be expressed by the regression equation: $\text{systole} = a - b (\text{rate})$, where a and b are constants. The factor b indicates how systolic duration alters with change in heart rate. The a and b values are different for each individual.

The median value found for b in aortic valve disease was 0.8 (4 cases), in mitral stenosis 0.6 (13 cases), and in mitral stenosis with insufficiency 0.6 (5 cases). In contrast, the median b value found in hypertension was 0.4 (13 cases),

in pure mitral insufficiency 0.2 (2 cases), and in uncomplicated arteriosclerotic heart disease 0.3 (5 cases). The b values in the first 3 groups, with 2 exceptions, were all higher than in the last 3 groups.

The reason proposed for this difference lies in the observed abolition of the rapid ventricular filling phase in mitral stenosis (due to inflow obstruction) and in aortic valve disease (due to reduced distensibility of the hypertrophied myocardium). In these patients, end-diastolic ventricular volume (and hence ensuing systolic duration) is more dependent on rate than in patients without impeded ventricular filling. Under such circumstances, high values for b obtain. In pure mitral insufficiency, despite a hypertrophied myocardium, the rapid filling phase is maintained by high atrial end-systolic pressure.

This new approach to the problem of the duration of systole offers an explanation for the conflicting findings of other workers who have emphasized the variability of a and assumed the relative constancy of b in all patients.

Anatomic Variations of the Auditory Canal Pertaining to the Fit of Stethoscope Earpieces

Dale Groom and Waddy Chapman, Charleston, S.C.

Leaks in the enclosed acoustical system of the stethoscope reduce its efficiency and can greatly impair the physician's ability to detect the faint murmurs of early valvular heart disease. To determine to what extent leaks may occur around conventional stethoscope earpieces, plastic casts of the external auditory meatuses of 10 medical students were made both with and without the earpieces in place.

Cross-sectional measurements of the casts showed the ear canals to be of elliptical shape in all subjects and to vary remarkably in size—from 11.8 x 8.0 mm. to 8.2 x 6.2 mm. Moreover, the angle of the axis of the canals varied as much as 43° in the vertical and 33° in the horizontal plane, causing partial or complete occlusion of earpiece apertures in more than half the subjects.

The amount of "give" of the ear structures is uncertain, but it would appear that effective stethoscope efficiency might be appreciably improved by more allowance for individual anatomic variations of the auditory canal in the design and fitting of stethoscope earpieces.

Renal Hypertension Induced by Partial Return of Urine to the Circulation

Arthur C. Guyton and William E. Bowls, Jackson, Miss.

Urine was returned to the circulation of dogs to 21 hours each day through indwelling catheters placed in the pelves of the kidneys and the vena cava. When the urine was returned as much as 8 to 21 hours each day, 2 patterns of results developed about equally in different dogs: (1) listlessness, failure to eat, vomiting, and other signs of toxemia followed soon by death, or (2) no signs of toxemia at first, but a gradual rise in arterial pressure over a period of 2 to 4 days, reaching a maximum elevation of 40 to 70 mm. Hg above the mean control. At this point toxemia often supervened, the pressure fell, and the dogs died. During the periods of urine flow to the exterior, the urinary outputs usually were 2 to 4 times normal. The purpose of these experiments was to show that hypertension can develop in animals with normal kidneys and with the kidneys not at all ischemic but, if anything, hyperemic. These experiments indicated that a critical reduction in renal output, even though the kidneys are functioning normally, can cause a hypertensive effect that is greater than the toxic effect and thereby result in hypertension. This could explain, even without implicating a renal ischemic hormone, the occurrence of hypertension in some stages of renal destruction while it does not occur in other stages.

Mechanism of Cardiogenic Shock

Santiago V. Guzman, Edward W. Swenson, Robert A. Mitchell, and Malcolm D. Jones, San Francisco, Calif.*

The mechanism of cardiovascular shock, following acute myocardial infarction, is still controversial. We utilized the technique of coronary artery catheterization in the anesthetized intact dog and injected embolizing agents (lycopodium spore and glass microspheres, 30-40 μ in diameter) into specific areas of the coronary circulation. During the embolization, we studied acute hemodynamic and electrocardiographic changes, and changes in coronary vascular bed, as demonstrated by roentgenographic and cinefluorographic techniques (using an image intensifier and 16 mm. movie, taken at 60 frames per second). Two coronary arterial catheters were inserted via the carotids: 1 into the anterior descending branch, and the other into the circumflex branch of the left coronary artery. One of the branches was embolized while the vascular pattern of the other coronary artery was studied by the injection of a radioopaque material.

Coronary embolization resulted in a marked decrease in cardiac output, hypotension to shock

level, elevation of pulmonary arterial and left atrial pressures, marked increase in total peripheral resistance, and electrocardiographic evidence of an acute myocardial injury. Coronary arteriograms showed a marked decrease in the size of the vascular bed of the nonembolized branch. These responses were not affected by bilateral vagotomy, but were partially blocked by atropinization.

The results suggest that the main factor responsible for the production of "cardiogenic" shock following coronary embolization is a decrease in cardiac output, and following embolization of 1 branch, coronary vasoconstriction occurs in the nonembolized branch.

Effect of Acute Salt Depletion upon Small and Large Blood Vessels

Francis J. Haddy, Chicago, Ill., and Malcolm Fleishman, Fayetteville, N.C.

Circulatory failure frequently accompanies electrolyte loss. Elkinton found low cardiac output and high peripheral resistance in experimental salt depletion. This study was initiated to determine: (1) which cations are affected in experimental salt depletion; (2) whether resistance does rise; and (3) its mechanism. Blood flow to 30 dog forelegs was held constant. Pressures were measured at 4 sites along the leg length. Salt depletion was produced by intraperitoneal administration of 5 per cent glucose. Average changes after 40 minutes were aortic pressure -30 mm. Hg, hematocrit +8 per cent, serum sodium -17 mEq. per L., potassium 0 mEq. per L., calcium +0.2 mg. per cent, magnesium -0.5 mg. per cent, arterial pH -0.01. Pressure changes in mm. Hg in 16 nerve intact forelegs were brachial artery +37, small artery +33, small vein 0 and cephalic vein 0. Pressure changes were similar in 9 nerve sectioned forelegs, but were absent in 4 of 5 adrenergically blocked legs. Pressure elevations were slightly antagonized by foreleg nerve section and greatly antagonized by adrenergic blockade or intravenous injection of 5 per cent glucose or hypertonic NaCl.

Hence, sodium is predominantly affected and peripheral resistance does increase. This increase results mainly from active arteriolar constriction, which is largely related to an adrenal discharge (decreased blood volume \rightarrow decreased venous return \rightarrow decreased cardiac output \rightarrow decreased arterial pressure \rightarrow decreased pressoreceptor activity \rightarrow sympathetic-adrenal discharge). It may also be related to direct effects of altered water and electrolyte concentrations upon smooth muscle cells.

Study of Gas Exchange in Stationary Screen Oxygenators

Edward R. Hagopian, George J. Haupt, John J. McKeown, Jr., and John Y. Templeton, III, Philadelphia, Pa.

The exchange of O_2 and CO_2 with blood filmed over a vertical stainless steel screen, 58 cm. high and 29 cm. wide, was studied. The screen, Tyler Ton-Cap No. 538, is a type widely used in heart-lung machines, as described by Gibbon. The relation of blood flow, film thickness and transit time to blood oxygen saturation were determined.

Fresh heparinized beef blood was deoxygenated to approximately 50 per cent saturation and the pH, carbon dioxide tension and temperature adjusted to normal values. The blood was pumped over 1 or 8 screens. Blood entering and leaving the oxygenator was analyzed for oxygen content, oxygen capacity, carbon dioxide content, pH and temperature. Oxygen saturation and carbon dioxide tension were calculated from these measurements. Blood flow rates of 125, 250 and 500 ml. per screen per minute were studied. A gas mixture of 97 per cent oxygen and 3 per cent carbon dioxide was passed through the oxygenator at a rate of 20, 10 or 5 L. per minute.

Sixty observations were made with 1 screen and 10 L. of gas flow per minute. The oxygen saturation of the venous blood ranged from 40 to 60 per cent and averaged 51 per cent. At flow rates of 125 ml. per minute, oxygen saturation was raised to an average of 94 per cent, at 250 to 87 per cent and at 500 to 76 per cent.

Fourteen observations were made with 1 screen and gas flows of 5 and 10 L. per minute. Fifteen observations were made with 8 screens and gas flows ranging from 5 to 20 L. per minute. No improvement in gas exchange was noted with gas flows over 5 L. per minute. The volume of blood on the screen was measured as 80, 119 and 170 ml. and the transit time was calculated as 39, 28 and 20 seconds at flows of 125, 250 and 500 ml. per minute.

Myocardial Metabolism During Elective Cardiac Arrest Determined by Biochemical Analysis of Multiple Cardiac Biopsies

David P. Hall, Robert G. Ellison, Walter Butler, Vidor Bernstien, and Sam A. Singal, Augusta, Ga.

Values for myocardial glycogen and lactic acid following potassium cardiac arrest were determined. The following experiments were performed in dogs: 1. In 3 experiments, biopsies taken from the right and left ventricles were analyzed for glycogen and lactic acid immediately following

arrest with 2½ per cent K citrate in blood. Seven experiments with biopsies from the right ventricle and 22 from the left ventricle 30 minutes and 90 minutes following arrest were analyzed. Cardiac arrest was induced with 2½ per cent K citrate and 10 per cent glucose in blood. 3. Six experiments with cardiac arrest for 15 minutes during cardiopulmonary bypass with pump-oxygenator. Biopsies were obtained immediately, 15 minutes after arrest, 15 minutes after resuscitation, and 5-15 minutes after coming off bypass.

Studies indicate that values for glycogen and lactic acid vary considerably. At this time, cardiac resuscitation appears better following arrest with K citrate in hypertonic glucose, although no biochemical differences have been detected. In group 2, 299 per cent increase in lactic acid and 69 per cent decrease in glycogen occurred after 90 minutes of arrest. In group 3, after 15 minutes arrest, glycogen had fallen 15 per cent and continued to fall to 50 per cent, 5-15 minutes after coming off bypass. Lactic acid increased 51 per cent during arrest and returned to 24 per cent above normal after bypass. This suggests the excessive use of glycogen immediately following resuscitation. Current studies are directed toward the use of ATP in the arresting solution, biochemical changes of ATP and phosphocreatine with arrest and biochemical studies during combined cardiac arrest and hypothermia.

Prediction of Downward Temperature Drift During Hypothermic Anesthesia

Charles A. Hamilton, Bismarck, N. D.

Accurate control of the fall of central body temperatures during immersion hypothermia is critical because temperatures below 30 C. are frequently associated with ventricular arrhythmias. Prediction of the downward drift of temperature after removal from ice water bath has been empiric. It is usually estimated at one-half to two-thirds the number of degrees of lowering at the time the cooling agent is discontinued.

This drift depends upon these interrelated factors: (1) body size and consistency; (2) activity of the thermoregulatory center, reduced by anesthesia; (3) activity of the circulation between peripheral and central tissues; and (4) gradient of temperature between peripheral and central tissues. Since the first 3 factors are relatively constant during drift in the method employed, the rate of fall of central body temperature and extent of drift should depend upon the fourth factor, the temperature gradient (as for a passively cooling body) and, therefore, should describe a logarithmic curve.

his hypothesis was tested by retrospective evaluation of the esophageal, rectal, and intramuscular temperature course of a group of 7 patients who had undergone hypothermia by immersion. The finding of straight plot lines for esophageal temperature drift verified the exponentiality of central body temperature drift. It was further tested by a study in which the surgical level of esophageal temperature was predicted prior to removal from the ice bath of another group of eight patients. The practical value of this prediction is that it is more reliable than the empiric method for anticipating surgical level of esophageal temperature in hypothermia.

Comparison Between the Ventricular Activation Process of Dog, Pig, Man and Sheep

Robert L. Hamlin, Charles R. Smith, and Richard W. Redding, Columbus, Ohio

The total ventricular activation process may be qualitatively derived by recording peripheral electrocardiograms, the axes of which determine, respectively, cranio-caudal, dorsoventral, and left-right forces, if one knows the relation of the cardiac structures within the torso to the respective lead axes.

Twelve individuals of each species (dog, pig, sheep and man) were studied by recording frontal, sagittal and horizontal plane QRS vectorecardiograms, and electrocardiograms I, aV_F and V₁₀ (unipolar lead from the dorsal spinous process of the seventh thoracic vertebra; also the back point of the vectorecardiogram system) simultaneously at 1,000 mm. per second.

All species had initial, low-magnitude septal forces directed equally ventrad and cephalad and slightly rightward. Ventricular free-wall activation followed in the dog and pig with high-magnitude strictly caudad forces, and in man with high-magnitude forces directed equally caudad and leftward. The sheep did not have these forces. All species had terminal basilar forces, directed equally dorsad and cephalad in the dog and sheep, markedly dorsad and slightly cephalad in the pig, and dorsad and slightly cephalad and rightward in the humans studied.

Considering the differences in position of the heart within the thoraces, the derived ventricular activation process of dog, man and pig are similar, with the exception of the pig's markedly dorsal terminal vector. This may be accounted for by incomplete penetration of Purkinje fibers into the basilar positions of the ventricular free walls. The sheep had an entirely different time course of ventricular free-wall activation due to complete penetration of Purkinje fibers into the epicardium of the ventricles.

Time Order of Ventricular Activation for Ventricular Premature Beats in Sheep and in Dogs

Robert L. Hamlin, Charles R. Smith, and Richard W. Redding, Columbus, Ohio

Average duration for the sinus QRS complex was 0.035 seconds for the sheep and 0.041 seconds for the dog. The average prolongation of premature beats was 145 per cent in the sheep and 210 per cent in the dog. Spatially, the mean QRS vector for both species was directed coplanar to the median sagittal plane—the sheep being minus 120 degrees at a magnitude of 0.8 mV. and the dog being at 88 degrees and a magnitude of 1.4 mV. In both species, premature beats from left ventricular foci were directed cephalically, and from right ventricular foci, caudally. It is difficult to explain why premature beats from identical foci in sheep and dog hearts have nearly identical mean spatial QRS vectors, yet the prolongation and magnitude is so much greater in the dog whose heart is less than 1/2 the size of the sheep's. Of the possible explanations for the data: (1) that the activation for premature beats is all muscle fiber to muscle fiber; (2) that the impulse quickly re-enters into the Purkinje system; or (3) that a combination of the 2 exists. The last is most tenable, based upon anatomic studies describing the more complete penetration of the Purkinje fibers into the epicardium of sheep.

Differentiation of Valvar and Subvalvar Aortic Stenosis

Ernest W. Hancock,* Boston, Mass.

Aortic stenosis was subvalvar in 16 per cent (16 of 100) patients studied at operation or by left ventricular puncture with withdrawal pressure records across the aortic valve. Under the age of 30, 43 per cent (13 of 30) were subvalvar. Four features enable this differential diagnosis to be made clinically: 1. Calcification of the valve specifically indicates valve stenosis; it is nearly universal in severe cases over age 30, but is rare under age 25. 2. Poststenotic dilatation of the aorta, if conspicuous, usually indicates valve stenosis. 3. An aortic ejection sound is almost always audible in noncalcific aortic valve stenosis, but in subvalvar stenosis is audible rarely, if ever. Phonocardiograms recorded with aortic and left ventricular pressures support the concept that the ejection sound is an opening snap of the aortic valve. 4. A normal arterial pulse contour in aortic stenosis of significant degree suggests a subvalvar stenosis of muscular type, or a valve stenosis with associated muscular subvalvar obstruction; an anacrotic type of pulse contour suggests uncomplicated valve stenosis, or rarely a fixed membranous subvalvar stricture.

Management of Coarctation of the Aorta During the First Year of Life

Franklin J. Harberg, Houston, Tex., and Elton Goldblatt, Johannesburg, South Africa

Thirty-eight patients with coarctation of the aorta, during the first year of life, were operated upon from June 1953 to June 1959 at the Hospital for Sick Children, London. All of these children had signs and symptoms of congestive heart failure. Surgery was indicated for 1 or more of the following reasons: (1) intensive medical management had been unsuccessful; (2) blood pressure was over 200 systolic or 100 diastolic; (3) there was electrocardiographic evidence of severe heart strain.

General anesthesia with the use of relaxant drugs was common practice for surgery. Resection with end-to-end anastomosis, utilizing a single continuous simple suture, was the technic. Twenty patients survived and have been followed from 3 to 26 months. Two patients were on maintenance digitalis 6 months and 14 months, postoperatively. In only 1 patient were femoral pulses lost in the postoperative period. Nursing care in the preoperative and postoperative periods contributed heavily to the final outcome in all these patients.

Eighteen in the group succumbed and post-mortem examination was obtained in 16 instances. Fifteen deaths were encountered in the first 48 hours, either from cardiac arrest during surgery, or progressive heart failure postoperatively. The other deaths occurred at 1 month, from congestive heart failure; at 2 months, from aspiration pneumonia; and at 4 months, from pneumonia. Additional major cardiac abnormalities, found at postmortem examination in 13 cases, included atrial septal defect, ventricular septal defect, hypoplastic aortic arch, anomalous systemic venous return, mitral stenosis and aortic valve atresia.

Oxygen Cost of Breathing: Simplified Technic

K. Albert Harden, R. G. Bartlett, Jr., Helen B. Barnes, William P. Waters, and Christina G. Carr, Washington, D.C.

The oxygen cost of breathing was determined by a simplified technic described by Bartlett, Brubach, and Specht. It utilizes a modified respirometer. This technic has the advantage that it includes the elastic resistance and viscous resistance of the chest wall, unlike the technic of using intra-esophageal pressures and tidal volume for determining the work of breathing.

Forty-one determinations among 28 normal subjects ranging in age from 21 to 32 years

yielded a mean value of 4.4 ml. of oxygen per L. of ventilation with a range of 2 to 9 ml., S. D. 1.60. These determinations were made at a voluntary ventilation rate of less than maximal and the mean value was 66.5 L. per minute, S. D. 20.9. The rate of breathing was approximately 40 per minute. Duplicate determinations were done on 12 individuals; in 6 cases these were identical and in the other cases there was no variation greater than 1 ml. Cournand and his co-workers predicted 3.2 ml. per L. at 80 L. of ventilation in the normal subject on the basis of parabolic curves.

Sarcoidosis (5 cases) 3.5 to 12 ml. per L. of ventilation; pulmonary emphysema (5 cases) 5 to 17.8 ml. per L. of ventilation; tuberculosis (5 cases) 4.4 to 19 ml. per L. of ventilation.

The results obtained in normal patients are highly reproducible and the results are significantly higher in patients with disabling pulmonary disease. The technic is simple enough for routine cardiorespiratory testing and appears to be adequate for clinical investigative work.

Cardiac Malformations in Rats Induced by Exposure of the Mother to Six Per Cent Carbon Dioxide During Gestation

Olga M. Haring, Chicago, Ill.

Exposure of pregnant albino rats to a gas mixture of 6 per cent carbon dioxide, 20 per cent oxygen, and 74 per cent nitrogen for 24 hours caused cardiac malformations in the offspring. The severe cardiovascular anomalies (truncus communis, transposition complexes, and interventricular septal defects with aortic dextroposition) were found only in the experimental group and not in the control group, and they occurred only when the mothers were exposed during certain periods of pregnancy.

The significant observations concerning these defects arose from a study of 400 serially sectioned experimental and 100 serially sectioned control hearts. Transposition complexes occurred in 19 out of the 137 rats exposed to increased carbon dioxide tensions from the eighth to the twelfth days of pregnancy (13 per cent), but not in those exposed earlier or later during pregnancy and not in the controls. Similarly the incidence of truncus communis was 13 per cent (19 of 123) in rats treated from the eleventh to the fifteenth days. Interventricular septal defects with dextroposition of the aorta occurred in 8.1 per cent (22 of 320) with exposure from the fifth to the tenth, and from the thirteenth to the seventeenth days. The incidence of both malformations was 0 in the control group.

The only defects noted in the hearts of the control animals were simple membranous septal defects which occurred in 7 per cent.

Acid-Base Abnormalities Encountered with the Gibbon-Mayo Pump Using Blood Flow Rates of 2-2.4 Liters per Square Meter of Body Surface per Minute

Ardis F. Hartmann, Jr., Albert Roos, and David C. Aldring, St. Louis, Mo.

The venous blood of postoperative patients who had undergone repair of serious congenital cardiac malformation, using the Gibbon-Mayo pump, showed profound acidemia, while the arterial oxygen saturation (earpiece oximeter) was well above 90 per cent. Clinical appearance seemed much worse than arterial oxygen saturation would indicate.

It was because of these discrepancies that the following studies were undertaken: 1. Thirty patients who had surgical repair of cardiac defects, using extracorporeal support, were studied. The following blood constituents were determined: pH, CO_2 , lactic acid, sodium, potassium, calcium, phosphorus, chloride, oxygen saturation and total and fractional proteins on the (a) donor blood, (b) blood in the pump prior to bypass, (c) arterial and venous blood of the pump at the end of bypass, and (d) femoral artery and vein blood of the patient 4 hours postoperatively. 2. The postoperative A-V difference studies were also carried out on 10 postoperative hypothermia patients and on a similar number of patients who had a unilateral thoracotomy for the repair of a patent ductus arteriosus or coarctation of the aorta.

Results. 1. The acidemia of the pump blood before and during bypass was mild and was due to the method of collection and processing of the donor blood. This was primarily due to stasis, glycolysis and dilution with saline. 2. The A-V difference of the pump blood at the end of bypass was in the normal range, indicating good circulation during bypass. 3. The A-V difference of the patient's blood 4 hours after bypass was marked. Similar studies in the posthypothermia and unilateral thoracotomy patients revealed only moderate changes. 4. These A-V differences indicate poor circulation in the extremity from which these samples were drawn. This could be accounted for by: (1) low cardiac output; (2) local vasospasm, or a combination of both.

Cardiorespiratory System of Calves: Physiologic and Anatomic Data Compared

Hans H. Hecht, Ramon L. Lange, William H. Barnes, and Hiroshi Kuida, Salt Lake City, Utah

The spontaneous occurrence of congestive heart failure at high altitudes in cattle has raised the

question of the relation of hemodynamic and respiratory responses to the morphologic structures of the cardiovascular and respiratory system. Twelve normal calves, aged 1 to 9 months, were studied by accepted physiologic methods and complete autopsies were obtained. The resting cardiac output varied from 8 to 43 L. per minute, stroke volume from 75 to 550 ml. per beat. Pulmonary "wedge" pressures varied from 5 to 10 mm. Hg. Pulmonary artery and systemic pressures were comparable to those accepted for human subjects. However, on slight provocation, pressure measurements in these animals reached values considered abnormal for man, with peak data of 50/15 mm. Hg for the pulmonary artery pressure and 170/145 for systemic pressures.

In consequence, both pulmonary arteriolar and systemic resistance values showed marked fluctuations throughout an experimental period. Even greater departure from data considered normal for adult human subjects was obtained for respiratory function: the minute ventilation was increased, with a tidal volume (V_T) but twice the volume of the physiologic dead space (V_D). The ratio V_D/V_T was almost 3 times that of human subjects. Although nitrogen wash out curves and arterial gas data were normal, alveolar ventilation was a much smaller fraction of the volume of the expired gas (V_E) that in man, a circumstance which should readily lead to alveolar hypoventilation.

The anatomic studies demonstrated in addition to the expected large respiratory dead space, a well developed muscular layer of pulmonary arteries down to arteriolar size of 20μ , suggesting a spiral muscular coat of low pitch surrounding the pulmonary arterial tree. Systemic arteries likewise demonstrated a heavy muscularis.

The relation of the gross and microscopic anatomic structure of the vascular system in calves seems adequate to explain certain hemodynamic and respiratory differences of this species when compared to man and allows some insight into mechanisms of altitude adjustment, pulmonary vasomotion, and heart failure.

Effect of Potassium Perfusion on Membrane and Action Potential of the Isolated Heart

Hans H. Hecht, Arthur S. Ruby, and George H. Carman, Salt Lake City, Utah

In resting heart muscle, a chemical gradient for potassium exists with the intracellular potassium concentration 30 times that of the extracellular surrounding. There is an obvious correlation between the differences in potassium concentration and the electrical potentials gradient between the intra- and extracellular space.

In the total excised and perfused bullfrog heart, stimulated at a fixed heart rate, the potassium

gradient can be reduced by increasing the potassium content of the perfusate with a concomitant change in the magnitude and the time course of the electrical potential simultaneously with the occurrence of the well-known "hyperkalemia" surface electrocardiogram. When the chemical gradient is reduced to two-thirds of the resting value, spontaneous irregularities occur which may become repetitive, leading eventually to ventricular fibrillation. It is assumed that the process is initiated by a re-entry phenomenon, related to an impairment of the depolarization process (conduction) and likely to be the consequence of the decrease in membrane potential. The effect of digitalis on membrane and action potential is similar to those observed after raising the external potassium content. This may be brought about by depleting the intracellular potassium stores; in either case a decrease in the chemical gradient across the cell membrane can be postulated. These interrelationships shed further light on the role of potassium in maintaining excitability, on the effect of digitalis on the electrical manifestation of the heart, on the nature of the ventricular gradient, and on the origin of cardiac irregularities.

Bacterial Endocarditis after Surgery for Congenital Heart Disease

Henry L. Heins, Jr., and Leonard M. Linde, Los Angeles, Calif.

Before the antibiotic era, subacute bacterial endocarditis (SBE) was almost invariably a fatal complication in congenital or acquired heart disease. With the onset of the antibiotic era, incidence and mortality decreased, but resistant bacterial strains soon emerged. Further changes have been noted in the clinical picture of endocarditis with heart surgery, and more recently after operations requiring the heart-lung machine. This report is prompted by the significant changes in endocarditis with regard to pathogenesis, clinical picture, bacteriology, treatment, and prognosis.

Seven instances of SBE following surgery for congenital heart disease are reported. In 5 of these patients, the extracorporeal heart pump was utilized in the surgical repair.

In a total experience of 144 cases of heart pump surgery for congenital heart disease, 5 cases, or 3.5 per cent, developed bacterial endocarditis, with 2 deaths. There were only 2 cases of SBE after other types of heart surgery. In these 7 cases, the usual classical signs and symptoms of SBE were not present. Fever, occurring soon after surgery, was often the sole clue which led to definitive diagnosis.

The offending bacteria were often unusual and included *Neisseria pharyngis*, *achromobacter*,

pseudomonas, and *Staphylococcus albus* and *aureus*. The increased virulence and resistance of these organisms made choice of antibiotics very crucial.

In SBE occurring after heart surgery, awareness of its frequency, atypical clinical picture, and unusual involved bacteria is necessary for prompt clinical diagnosis and therapy.

Experimental Circulatory Arrest at High Atmospheric Pressures of Oxygen

John Helwig, Jr., and Charles C. Wolfert, Jr., Philadelphia, Pa.

At present, open heart surgery is performed with either extracorporeal circulation, hypothermia, or both. Theoretically, it might be possible to prolong the period of tolerable circulatory arrest if the tissues had been presaturated with oxygen. To test this principle Boerema, in 1956, reported recovery of rabbits following inflow occlusion for as long as 45 minutes, employing hypothermia and oxygen breathing at 3 atmospheres.

The present experiments were done in a pressure chamber with normothermic dogs breathing 100 per cent oxygen at 4 atmospheres. Inflow occlusion and inflow-outflow occlusion were utilized. The blood pressure, electrocardiogram and electroencephalogram were recorded.

Eleven dogs were studied. Of the 4 subjected to both inflow and outflow occlusion of 15 minutes or more, all developed ventricular fibrillation and the only one that could be resuscitated survived for 48 hours with decerebrate rigidity. Four dogs had inflow occlusion alone for 15 minutes. Two developed ventricular fibrillation and were successfully resuscitated. All but 1 had massive brain damage and were dead within 72 hours. Three dogs had inflow occlusion alone for 10 minutes. All but 1, who died accidentally, survived with minimal brain damage. All dogs developed marked electroencephalographic depression within 1 minute of occlusion. All animals in a control group with inflow occlusion alone for 15 minutes died within a few hours with massive brain damage. These preliminary results suggest that tissue supersaturation with oxygen as a single measure will not afford a useful degree of protection.

Clinicopathologic Correlations in Coronary Artery Disease at the Boston City Hospital: Preliminary Report

Ernest A. Higgins, Jr., John P. Leddy, Felix L. Rodriguez,* and Laurence B. Ellis, Boston, Mass.

Findings in 100 random adult hearts (53 per cent male), studied by Schlesinger's technic, were correlated with clinical data. There were 30 infarcted hearts, all but 7 of which showed coronary

clusions. Only 1 occlusion occurred without infarction. Atherosclerosis was present as follows: severe cases (including 24 with occlusions), 23 moderate, 11 mild, 20 none. Cases with severe atherosclerosis were compared to those without sclerosis with respect to: cardiac hypertrophy, 55 per cent vs. 17 per cent; heart failure, 68 per cent vs. 53 per cent; hypertension, 50 per cent vs. 30 per cent.

Eleven patients had clear-cut angina; all showed infarctions and severe sclerosis, and all but 2 had occlusions. Half of the 18 cases with 1 or more old major occlusions had no angina. Clinical diagnosis of infarction was confirmed in 78 per cent of 27 cases. Of 29 old infarctions, 12 had not been suspected clinically. Three acute and 6 old infarctions occurred in patients not clinically suspected of coronary disease. The electrocardiogram missed 6 infarctions (2 acute) and falsely diagnosed 2 (acute). Eighty per cent of 20 patients with clinical coronary disease had occlusions. Sixty-four per cent of patients with moderate to severe sclerosis lacked clinical criteria of coronary disease.

The sample agrees with Blumgart et al. in regard to the incidence of occlusions and angina, but differs in the frequent occurrence of infarction without occlusion, the rarity of occlusion without infarction, the equal severity of occlusive disease with or without angina, and the absence of angina without infarction. Generally, the diagnosis of coronary disease was reliable only when infarction existed.

Concealed Conduction: Sites and Mechanisms

Brian F. Hoffman, Paul F. Crane, Paul F. Jackson, H. Stuckey, Norman S. Amer, and Rodolfo T. Domingo, Brooklyn, N.Y.

Multiple intracellular microelectrodes have been used to record from single fibers of the atrium, atrioventricular node, and His bundle of the isolated rabbit heart. Multiple small differential electrodes have been used to obtain simultaneous records directly from the His bundle, bundle branches, and peripheral Purkinje fibers of the in situ dog heart during total cardiopulmonary bypass. Conduction delay or failure of A-V transmission has been induced by changing atrial or ventricular rate or by initiating atrial or ventricular extrasystoles. Abnormal delay or failure of A-V conduction has been demonstrated at the atrial margin of the A-V node; within the A-V node; and in the His bundle, right and left bundle branches and peripheral Purkinje fibers. Failure of transmission of excitation within the A-V conducting system has been shown to occur both with and without delay of transmission of subsequent

activity. Conduction delay or block has resulted from changes in the action potential of fibers at the atrial margin of the node, changes in the action potential of fibers within the node, or the normal increase in action potential duration from the His bundle to peripheral Purkinje fibers. Prolongation of electrical activity by nonpropagated local responses has also been shown to cause subsequent delay or failure of A-V transmission.

Antihypertensive Effect of Spironolactone (SC-9420), Steroidal Antagonist

William Hollander and Aram V. Chobanian, Boston, Mass.

Previously reported studies on a spironolactone SC-8109, an aldosterone antagonist, indicated that such compounds might be useful as antihypertensive agents. Therefore, spironolactone (SC-9420) a more potent steroidal antagonist, was studied in 32 hypertensive subjects in daily oral dosages of 150 to 400 mg.

Spironolactone alone reduced blood pressure in 6 of 12 hypertensive subjects by 15/10 to 65/35 mm. Hg, but had no hypotensive effect in 10 normotensive subjects. When added to other antihypertensive treatment, it further reduced blood pressure in 15 of 20 subjects by 15/10 to 55/30 mm. Hg. Spironolactone was well tolerated and caused no noticeable serum electrolyte or BUN disturbances. It restored serum potassium to normal in all cases in which it had been reduced by chlorothiazide.

Metabolic studies in 8 subjects indicated that: 1. Spironolactone blocks the renal excretory effects of desoxyeorticosterone on sodium and potassium. 2. The antihypertensive effect of spironolactone is associated with negative sodium balance of 147 to 258 mEq. and slightly positive potassium balance of 45 to 98 mEq. 3. A reduction in plasma volume occurs in one-half the treated cases. However, during spironolactone (as during chlorothiazide) treatment, experimental over expansion of plasma volume by plasma infusion, or correction of negative sodium balance by saline infusion, does not abolish its antihypertensive effect.

Results. 1. Spironolactone is an effective antihypertensive agent which does not produce hypokalemia, but can correct hypokalemia produced by chlorothiazide. 2. Its antihypertensive effect, like that of chlorothiazide, is not due solely to depletion of body sodium or plasma volume.

Effects of an Inhibitor of Cholesterol Biosynthesis, Triparanol (MER-29), in Subjects with and without Coronary Artery Disease

William Hollander, Aram V. Chobanian, and Robert W. Wilkins, Boston, Mass.

Triparanol (MER-29), a cholesterol-lowering agent which structurally resembles a synthetic estrogen chlorotrianisene but does not cause feminizing effects, was given to 50 subjects with and without vascular disease intermittently for 7 months at an oral dosage of 250-750 mg. per day. The decrease in serum cholesterol averaged 48 mg. per cent and ranged from 20-110 mg. per cent in 43 of the 50 subjects and occurred without a change in serum phospholipids, weight or blood pressure.

The miscible pool of cholesterol, as calculated from the disappearance rate of intravenously administered C^{14} -labeled cholesterol decreased on the average by 41 per cent after triparanol. Triparanol also decreased by 32 per cent the rate of conversion of intravenously administered C^{14} -labeled acetate, a precursor of cholesterol, to cholesterol. Urinary 17-ketosteroid excretion did not change significantly, whereas corticoid excretion decreased slightly following triparanol treatment.

In repeated "two-step" exercise tests during the control period, 9 of the 15 subjects with angina pectoris developed reproducible pain and abnormal electrocardiographic changes. After 1 to 3 months of triparanol treatment, 3 of these 9 patients studied serially failed to develop angina or the adverse electrocardiographic changes found previously after the same amount of exercise. On the withdrawal of triparanol, the angina and electrocardiographic changes reappeared on exercise. Three other subjects had less frequent anginal attacks during triparanol treatment.

Triparanol is effective in reducing both serum and body cholesterol by interfering with the biosynthesis of cholesterol. The improvement in angina pectoris and the electrocardiographic tracings suggests triparanol may improve the adequacy of coronary circulation.

Localization of Arterial Obstruction

H. Edward Holling, H. Christine Boland, Philadelphia, Pa., and Ellier Russ, Bordentown, N.J.

Treatment of peripheral vascular disease by arterial grafting or thromboendarterectomy requires localization of the arterial obstruction. With this object in view, the clinical use of the mercury-in-rubber strain gage has been investigated. This instrument consists of a fine bore rubber tube filled with mercury and fixed closely around the limb at any desired level. An increase in the girth of the limb stretches the tube and increases the electrical resistance of the column of mercury within it. These changes are electrically recorded and interpreted as changes in limb volume. The system is sufficiently sensitive to record pulse volume changes without distortion and can act as a quantitative oscillogram.

The strain gage was used in 3 different ways. 1. Blood pressure cuffs were placed at different levels down the limb and arterial pressure at each level was measured. This was done by using the strain gage record from the foot to show a steady rise in volume when the cuff pressure had been slowly deflated to less than systolic. The pressure gradient down the leg aided in finding the distribution of arterial obstruction. 2. The amplitude and form of volume pulse tracings at different levels down the limb were also found to aid in localizing the arterial obstruction. 3. Blood flow measurements in the resting limb distal to occlusion were not found to be informative, presumably because of compensatory vasodilatation.

The results obtained have been compared to the localization of arterial obstruction as shown by arteriography.

Experiences with Open Heart Surgery in Pulmonic Stenosis with Right Ventricular Hypertension in Excess of 200 mm. Hg

George R. Holswade, Mary Allen Engle, Daniel S. Lukas, Frank Glenn, and Henry P. Goldberg, New York, N.Y.

Pulmonic stenosis with normal aortic root can usually be corrected satisfactorily and safely. Our experience with open heart surgery in patients with extreme stenosis and right ventricular hypertension in excess of 200 mm. Hg leads us to believe that this group still presents a problem in correction. Six such patients, aged 13 months to 21 years, were operated upon, and 3 died. The first 3 operations were performed under hypothermia (30 C.) and the others with use of extracorporeal circulation.

Three survivors, under 6 years of age, successfully underwent valvotomy for valvular pulmonic stenosis with accompanying infundibular muscular hypertrophy. The deaths were in a similar patient and 2 with infundibular stenosis only. A 7-year-old boy developed cardiac arrest in the recovery room after a satisfactory valvotomy under hypothermia. An 18-year-old girl died of unrelieved severe obstruction when her condition could not be corrected under hypothermia. At a previous transventricular operation and a post-operative cardiac catheterization, her stenosis was considered to be valvular. Instead, she had subvalvular stenosis due to a fibrous endocardial ring, with marked hypoplasia of infundibulum, pulmonary valve ring and leaflets. The third patient, aged 21, had infundibular pulmonic stenosis and corrected transposition of the great vessels. The obstructing tissue was excised with aid of extracorporeal circulation. The gradient decreased satisfactorily, but she died 3 days later. Post mortem studies in the 3 showed marked right ventricular hypertrophy and pulmonary edema.

These patients illustrate some problems that remain in localization of stenosis, extent of surgery desirable, and postoperative management.

Antihypertensive Effect of Kidney Transplants

Sibley W. Hoobler, Pedro Blaquier, and Arthur Gomez, Ann Arbor, Mich.

In all of 26 rats with renal hypertension and with DCA hypertension of less than 6 months' duration, the transplantation of the kidney from a normal rat resulted in an immediate decline in blood pressure to normal, but not to hypotensive levels. The blood pressure rose again when the transplant was excluded from the circulation. On the other hand, when the hypertension had existed for more than 6 months, insertion of the kidney frequently failed to lower the blood pressure. No depressor effect was observed when the recipient animal was made hypertensive with renin or angiotensin infusion, or when the hind-limb or a vascular shunt of low resistance was transplanted.

These studies indicate that the protective action of the normal kidney extends to several varieties of early hypertension and that the chronic phase may be maintained by a different mechanism, either structural or compensatory in nature. The rapid and predictable response of the rat to such renal transplants provides a new and useful technique for study of the mechanism of the protective action of the normal kidney.

New Technic for Performing the Vasodilatation Test

Orville Horwitz, Diane G. Abramson, and Anne M. Ayres, Philadelphia, Pa.

The vasodilatation test, the measurement of digital blood flow when vasomotor tone is abolished, serves as a measurement of collateral circulation in the presence of arterial occlusion. Frequently it is the determining factor in deciding whether arterial surgery should be attempted. When the test shows a good capacity for blood flow the limb is in no immediate danger, and a surgical procedure is usually contraindicated. Conversely with a poor capacity for flow the limb is in jeopardy and arterial surgery should be undertaken if feasible.

The blood flow in the toes is estimated by measuring the skin temperature with thermocouples while the feet are exposed in a 20 C. room. Heretofore, peripheral vasodilatation was induced by heating the body only, with heating pads and blankets. The average time to complete the test was about 2 hours. We have adopted a method of releasing the vascular tone initially by warming the entire body including the feet, by placing an additional heating pad close to, but not directly on, the feet and covering both with a blanket. By

making certain that the feet were never heated to a higher temperature than 38 C. we have tested over 250 patients without harmful incident. To encourage further blood flow to the feet, the head of the bed was elevated on 6 inch blocks thereby placing the feet in a slightly dependent position.

With these modifications we found that the test was shortened by an average of 24 minutes and that a fuller degree of vasodilatation occurred.

Rheumatic Fever Prophylaxis with Oral Erythromycin in Adults

Irene Hsu, John M. Evans, and Monroe J. Romansky, Washington, D.C.

During the past 4 years, a group of 50 adults with rheumatic heart disease was given erythromycin, 250 mg. twice daily, for rheumatic fever prophylaxis. Each patient was followed with periodic throat cultures, antistreptolysin O titers and the acute phase reactants.

Gastrointestinal disturbance occurred in 12 patients (24 per cent) necessitating a decrease in the dosage in 8, and discontinuance of the drug in 5. There were no other side effects.

At the present time, 12 patients have been followed through 3, and 3 patients through 2, streptococcal seasons, and in addition were able to come in regularly at monthly intervals for clinical evaluation and for performance of laboratory tests.

The present report deals with these 15 patients. Twelve are in class 1A of the New York Heart Classification, and 3 in class 2B. Prior to antibiotic therapy, β -hemolytic streptococci were cultured from 2. Five were judged to have rheumatic activity.

During the past 3 streptococcal seasons, streptococcal infection, manifested by a rise in the antistreptolysin titer, occurred in 4 patients. One of these was taking only 200 mg. of erythromycin a day. In 1 other, group A streptococci appeared in the throat culture during a mild sore throat. There has been no apparent progression of the heart disease.

Since 5 of the 15 patients had evidence of streptococcal infection and rheumatic exacerbation occurred in 1 of the 5, it would appear that erythromycin, in the dosage used, falls short of an ideal prophylactic agent.

Clinical Acidosis Due to Lactic Acid

William E. Huckabee,† Boston, Mass.

Twenty-five hospital patients with reduced serum CO_2 exhibited marked elevations of blood lactate rather than any of the previously known causes of acidosis. Two types of lactic acidemia were recognized: (1) those with commensurate eleva-

tions of blood pyruvate; and (2) those in whom the lactate was disproportionately large, relative to pyruvate. Group 1, whose blood findings thus indicated no tissue hypoxia, included patients who had received large doses of insulin, glucose or epinephrine or who were hyperventilating. All recovered. Group 2, whose findings, on the contrary, indicated that cellular hypoxia was the basic cause, was composed of patients with respiratory abnormalities (arterial O_2 saturations less than 85 per cent) who responded to O_2 administration; and patients whose hypoxia was not respiratory (arterial blood fully saturated, peripheral A-V O_2 differences normal or large). The latter patients had severe acidosis (lactates 18 to 25 mEq. per L. and CO_2 reduced to 6 to 10 mEq. per L.), and all died. No common element could be found in their clinical pictures, and the diagnosis of lactic acidosis could be made only by laboratory findings. Despite circumstantial evidence that hypoxia was probably caused by inadequate effective blood flow in some area, blood pressures and pulses were normal. Patients with severe congestive heart failure or shock did not exhibit significant lactic acidosis. The acidotic syndrome could not be reproduced in animals with various kinds of O_2 lack, including acute shock, but it could be produced by gradual prolonged reduction of blood volume with maintenance of cardiac output by epinephrine infusion, suggesting that peripheral vasoconstriction might be responsible.

Effect of Posture and Exercise on Plasma Volume

Lloyd T. Iseri, Downey, Calif., Milton G. Crane, Los Angeles, Calif., Etele L. Balatony, and John R. Evans, Downey, Calif.

In order to understand, more fully, the mechanism of salt and water retention in congestive heart failure, plasma volumes of 20 cardiac patients were serially determined in supine and standing positions, following a single injection of radioiodinated serum albumin (RISA). After obtaining a constant disappearance slope between the twentieth to the fiftieth minute following the injection, each subject was exercised for a given period and then put to rest again in the standing and supine positions. Serial hematocrit, plasma osmolarity and plasma radioactivity were determined.

Plasma counting rate increased with change in position from supine to standing posture. Exercise caused a transient increase in the counting rate independent of posture or venous pressure. Returning the patient to a supine position after exercise caused a decrease in plasma counting rate, often below the previously determined slope. Simultaneous determinations of arterial hematocrit followed, in general, the changes in plasma count-

ing rate. Simultaneous determinations of total plasma osmolarity (freezing point method) showed an increase with exercise. Peripheral venous and right atrial pressures often rose with exercise, but these measurements did not correlate with the aforementioned changes.

These findings indicate that: (1) plasma volume decreased on assuming an erect position, probably due to passive congestion and elevation of capillary pressure; (2) exercise produced a further decrease in plasma volume, presumably by transfer of water out of the vascular compartment; and (3) gain of plasma fluid in the supine position was of significant degree to suggest a mechanism for orthopnea in cardiac patients.

Approach to Roentgenologic Quantitation of Pulmonary Artery Pressure in Mitral Stenosis

Philip M. Johnson, Ernest H. Wood, Chapel Hill, N.C., and Morris Jones, Gainesville, Fla.

An investigation was made of the correlation between the mean resting pulmonary artery pressure, as determined at cardiac catheterization, and the magnitude of 3 variables objectively determined from the erect 2 meter posteroanterior chest roentgenogram. A total of 51 pressure observations in 48 patients having pure or predominant mitral stenosis were included in this study. The roentgenologic variables were: (1) the presence or absence of basal septal pulmonary lines (lines B of Kerley); (2) the width in millimeters of the descending branch of the right pulmonary artery; and (3) the altitude in millimeters of the second most cephalic convexity of the left cardiac border.

For analysis of these data, statistical models were constructed on the hypothesis that, in mitral stenosis, an individual's mean resting pulmonary artery pressure is a function of the 3 roentgenologic variables. A model was found by which it was possible accurately to discriminate between the 16 observations in which the mean resting pulmonary artery pressure was 50 mm. Hg or greater, and the 35 observations in which the value was less than 50 mm. Hg. In addition, a formula was evolved by which the numerical value of the mean resting pulmonary artery pressure could be predicted in 72 per cent of cases with a standard error of estimate of ± 10 per cent.

Earlier attempts to quantitate pulmonary pressure by purely roentgenologic criteria are reviewed.

Effect of Lipemia on Tissue Oxygen Tension

Claude R. Joyner, Orville Horwitz, and Phyllis G. Williams, Philadelphia, Pa.

Previous work has shown that intravenous fat infusion decreases myocardial oxygen tension in dogs having experimentally produced myocardial

in variation. Also, attacks of angina pectoris have been precipitated at rest near the peak of postprandial hyperlipemia. In the present study, the effect of varying levels of lipemia upon tissue O_2 tension (skin of toes) was determined in 12 subjects. Six had normal blood flow, and 6 had decreased capacity for flow as measured by vasodilation test.

Lipemia was induced by a fat meal. Twenty mg. heparin or 1 ml. saline was injected near peak lipemia. In 8 subjects, O_2 tension increased by 50 to 56 per cent coincident with heparin induced clearing of lipemia. When saline was substituted for heparin on a subsequent day, plasma lactescence did not change and O_2 tension decreased slightly. Injections of 20 mg. heparin when plasma was "clear" subsequent to 16 hour fast produced no change in O_2 tension. In 4 other subjects, lipemia did not change and O_2 tension remained constant or decreased after 1.5-2.5 mg. heparin or saline was injected at the peak of lipemia. However, O_2 tension increased 29 per cent in 1 subject studied during a 40 minute period of rapid spontaneous clearing of lipemia.

Therefore, tissue oxygen tension in man, as in the dog, appears to be influenced by the level of lipemia. We have no evidence that this effect resulted from change in blood flow. Room temperature and skin temperature of the toes remained constant during each study. Interference with oxygen diffusion appears to be a more probable explanation for these observations.

Demonstration of a Pressor Substance in Renal Vein Blood in Patients with Arterial Hypertension

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By means of spirally cut strips of rabbit thoracic aorta, constrictor activity could be assayed in 1-2 ml. of unfractionated, dialyzed plasma obtained by catheterization of the renal vein. In most of the patients cardiac output (Fick), renal blood flow (PAH), glomerular filtration rate (inulin), and electrolyte and water excretion were measured. In patients with unilateral renal disease, differential renal hemodynamic and excretory studies were accomplished.

Plasmas from patients with malignant or accelerated phase of hypertension caused a strong contraction. In addition, in this group the constrictor substance could be detected in blood from the vena cavae and peripheral artery. A decrease in the degree of constrictor activity of the plasma from the renal vein was observed in 2 patients in whom the blood pressure had been effectively lowered by antihypertensive agents. In patients with chronic hypertensive disease, a lower degree of constrictor activity was found. While in general the patients with a lower renal plasma flow and cardiac out-

put and higher arterial pressure tended to have greater amounts of constrictor substance, this relationship was not consistent.

The constrictor substance differs from the pressor amines in that it is heat labile, nondialyzable, and not blocked by adrenolytic agents. On the aortic strip, the response is similar to angiotensin. On incubation with red cell angiotensinase, the active principle is inactivated. Its behavior and properties are similar to renin and/or the sustained pressor principle.

Effects of Vasopressor Amines and Phenothiazine Derivatives on Experimental Shock

Robert E. Kalina, Philip L. Eckman, and Joel G. Brunson, Minneapolis, Minn.

A previously described method for producing stress shock by rotation in a modified Noble-Collip drum was used in 566 rabbits. A period of 30 minutes in the drum (800-900 revolutions) invariably was found to be lethal for untreated rabbits. Administration of vasopressor amines proved ineffective in preventing lethality. However, the lethality of the procedure was markedly decreased when certain phenothiazine derivatives were administered alone or in combination, before or during rotation. Although considerable variation was noted among the various drugs, WY 1359, promazine, promethazine and chlorpromazine proved highly effective. A survival rate of 86 per cent (12 of 14 animals) was obtained by immediate pretreatment with WY.1359, or by 1 hour pretreatment with a combination of promazine and promethazine. Hemorrhagic and ischemic lesions were observed in sections from the hearts, gall bladders, and intestines of the animals in all groups. Lesions consisting of areas of focal to diffuse hepatic necrosis were limited to those animals given sympathomimetic amines. Several mechanisms through which the phenothiazine derivatives prevent the lethality of the shock procedure may be postulated. These include alteration in body temperature, chemical changes in the blood, blocking of sympathetic response, and maintenance of capillary integrity.

Relationship of the Electrocardiogram to the Potassium Content of Red Blood Cells

Selwyn A. Kanosky, Joseph H. Boutwell, Louis A. Soloff; and with the technical assistance of Doris Rowell, Philadelphia, Pa.

The potassium content of red blood cells was measured to learn if this determination correlated better with electrocardiographic evidence of potassium depletion than did the level of serum potassium.

Seventeen persons, 13 with cardiac disease, had normal levels of potassium in serum and in red

blood cells and no electrocardiographic evidence of potassium depletion. One gram chlorothiazide daily for 5 to 8 days failed to produce detectable changes in these 3 parameters in those without heart disease.

A similar regimen in 5 with cardiac disease dropped the level of serum potassium significantly below normal without change in the other 2 parameters. However, when this regimen was continued beyond the tenth day, the level of potassium in red cells fell and the electrocardiogram revealed evidence of potassium depletion. Continuation of this regimen for 2 more weeks produced a steady but slow fall in red cell potassium and increasing electrocardiographic evidence of potassium depletion. At the same time, the serum potassium slowly rose to low normal.

Six had normal or high level of serum potassium and low levels of red cell potassium. One apparently healthy old woman with a past history of diverticulitis had electrocardiographic evidence of potassium depletion. The other 5 had heart disease. One had P.A.T. with block. Two others had electrocardiographic evidence of potassium depletion. The remaining two were terminal with tachycardia and a rising S-T (U?) segment merging with the succeeding P wave. One had uremia and the other had been on large doses of prednisolone.

Two others with P.A.T. with block and 1 with complete heart block, runs of ventricular tachycardia and multiple premature beats had normal levels of potassium in serum and red cells. These 3 responded to increased doses of digitalis by restoration of sinus rhythm in the first 2, suppression of ventricular arrhythmias in the third and clinical improvement in all 3.

Electrocardiographic manifestations of potassium depletion are associated with low levels of red blood cell potassium, whether the serum potassium is low, normal or high. Low levels of red blood cell potassium are usually associated with electrocardiographic manifestation of potassium depletion. However, this association may not be recognizable if the final deflection cannot be analyzed or may be absent in hypocalcemia. The level of potassium in red blood cells may differentiate P.A.T. with block due to digitalis intoxication from that due to intrinsic myocardial disease.

Retrograde Transpulmonary Propagation of the AC Wave in Mitral Stenosis

Ruebin Kaufman and David C. Levinson, Los Angeles, Calif.

A case is reported of a 51-year-old man with mitral stenosis, in whom retrograde transmission of giant, fused, left atrial AC waves through the pulmonary capillary bed occurred during cardiac catheterization, with reflection of these waves in the pressure contours of the proximal pulmonary vascular tree. The wedged pressure was 18/3 mm. Hg (mean, 8 mm. Hg), and the main pulmonary artery pressure was 32/12 mm. Hg (mean, 21 mm. Hg). A wave approximately equal in amplitude to the wedged AC wave was seen on the ascending limb of the systolic ejection wave in pressure pulses obtained from the near wedged right pulmonary artery, right main pulmonary artery and main pulmonary artery. The peak of the transmitted wave occurs 0.08 of a second after the peak of the QRS complex in the wedged and near wedged positions, 0.11 of a second in the right main pulmonary artery and 0.12 of a second in the main pulmonary artery. The pulmonary vascular resistance was 152 dynes seconds/cm.⁵ The electrocardiogram revealed incomplete right bundle-branch block and vectorcardiography showed terminal delay in the QRS loop, to the right, but was otherwise normal. The factors which may be responsible for the propagation are: increased pulmonary vascular tone, normal pulmonary vascular resistance, ventricular asynchronism secondary to right bundle-branch block.

Ruptured Mycotic Aneurysm of the Extremities

Edward B. C. Keefer and Lester Blum, New York, N.Y.

With increased aging of the population, the less common manifestations of arteriosclerosis are more frequently encountered. This seems to be true of that morbid state known as mycotic aneurysm, which in the past has been of prime interest to the pathologist. The disease process is characterized by the symptoms of sepsis and the dramatic sequelae of arterial rupture. When the location is visceral, mediastinal or retroperitoneal, the clinical picture usually develops too rapidly for successful surgical intervention. In the extremities, however, prompt recognition may permit the saving of life and limb.

The authors wish to present 5 cases of their own. In 4, the femoral artery was involved in Hunter's canal. In the fifth, the site was in the popliteal artery. Two cases ultimately suffered thigh amputation while artery grafting was possible in 3. All 3 showed positive wound cultures postoperatively, and 1 of these experienced 8 episodes of hemorrhage requiring as many re-graftings before success was achieved.

It is evident that the chief problem is that of infection. In 3 cases the organism was staphylococcus and in 2, salmonella. It is essential to make the diagnosis before the tissues are saturated with organisms and devitalized by the mounting pressure of the escaping blood. All fertile patients with a tender, indurated mass along the course of a major artery, whether pulsatile or not, should be carefully examined and followed on suspicion of having a mycotic aneurysm.

Pulmonary Vascular Effects of Bronchoconstrictor Drugs

Kaye H. Kilburn, Denver, Colo.

Because the volume of air in the lungs can alter intrathoracic pressure and hence, conceivably, modify the pulmonary vascular resistance, bronchoconstrictor drugs which also decrease pulmonary arterial (PA) pressure might act by this mechanism.

The cardiopulmonary responses to various doses of acetylcholine, histamine and serotonin were measured in 6 lightly pentobarbitalized dogs, which had pressure recording catheters in pulmonary "wedge" and artery and a femoral artery. Pneumotachygraph, esophageal balloon pressure recorder and a spirometer permitted estimation of lung compliance and volume changes. Drugs were injected into the right atrium.

Acetylcholine (0.12-2.0 mg.) produced apnea, cardiac asystole and a decrease of 50 per cent in systolic and 65 per cent in diastolic arterial pressure. PA pressure rose subsequently 16 per cent (2 mm. Hg) and pulmonary compliance decreased 22 per cent, with a 30 per cent decrease in tidal volume. The latency of these changes suggested that they followed peripheral action of the drug.

Histamine (0.04-0.12 mg.) lowered systolic arterial pressure 32 per cent and diastolic 38 per cent and raised PA pressure 20 per cent (3 mm. Hg). Tidal volume fell 56 per cent and compliance fell 34 per cent after 1 maximal inspiration.

Serotonin (0.12-2.0 mg.) produces tachypnea in 4-10 seconds, followed by slow, shallow breathing. Both systolic and diastolic arterial pressure rose 26 per cent and PA pressure doubled (11-23 mm. Hg) after doses above 1 mg. Tidal volume and pulmonary compliance decreased to 16 per cent and 30 per cent of controls following this dosage. Pulmonary "wedge" pressure mirrored esophageal pressure without paradox with all dogs.

Pentobarbitalized dogs respond to bronchoconstrictor drugs with decreased arterial pressure

and increased PA pressure. Such findings contrast sharply with men in whom both acetylcholine and histamine lower PA pressure. Serotonin acts similarly in man and dog to constrict both the bronchial tree and the PA system.

Comparative Effects of Pneumothorax on the Pulmonary Ventilation, Circulation and Diffusing Capacity of Anesthetized and Conscious Dogs

Kaye H. Kilburn, Denver, Colo.

Pneumothorax equal to 1 functional residual capacity (FRC) has been reported to decrease cardiac output and increase ventilation and pulmonary vascular resistance in anesthetized dogs. Because these changes are not observed in humans treated by pneumothorax, various parameters of cardiopulmonary function were measured up to 6 hours after a 2 FRC pneumothorax in conscious, compared to anesthetized, dogs. In addition, the steady state carbon monoxide diffusing capacity (DCO) was measured to determine if membrane characteristics were altered.

The FRC was determined by an open circuit helium method. Vascular pressures were monitored by conventional methods. The cardiac output was estimated by direct Fick after expired air was analyzed by micro-Scholander and blood gases by Van Slyke techniques. DCO was estimated by Filley's steady state technique, using an infrared CO analyzer.

In 14 anesthetized dogs, pneumothorax for 6 hours did not change cardiac output from 3.3 L. per minute (mean), but pulmonary artery pressure rose 5 mm. Hg mean difference (m.d.) and ventilation rose from 4.9-11.9 L. per minute with a fourfold rate increase, while $p\text{CO}_2$ fell 14 mm. Hg (m.d.). DCO fell initially, but returned to prepneumothorax levels of 8 ml. per minute per mm. Hg.

Pneumothorax in 6 conscious dogs, lowered cardiac output 28 per cent m.d. and minute ventilation 3 L. per minute m.d., but did not alter pulmonary artery pressure or $p\text{CO}_2$. DCO remained at prepneumothorax levels of 15 ml. per minute per mm. Hg.

Anesthetized dogs without pneumothorax increased ventilation 2 L. per minute (m.d.) and DCO from 10.3-16 ml. per minute per mm. Hg m.d., while cardiac output and $p\text{CO}_2$ fell slightly.

Conscious dogs fail to evidence hyperventilation, increased pulmonary resistance and decreased DCO when given 2FRC pneumothoraces. Pneumothorax and anesthesia appear to add up to produce alveolar hypoventilation and increased pulmonary vascular resistance, despite apparent hyperventilation.

Pulmonary Capillary Blood Flow Measured by the Plethysmographic Nitrous Oxide Method Compared with the Cardiac Output Measured by the Direct Fick Method

Philip Kimbel, Hakan Linderholm, David H. Lewis,† Marvin A. Sackner, and Arthur B. DuBois,† Philadelphia, Pa.

The plethysmographic nitrous oxide method for measurement of pulmonary capillary blood flow requires only that the patient be in an airtight chamber and hold his breath 10 seconds after inspiring 80 per cent M_2O ; alveolar air is sampled with an infrared analyzer, and pressure change (volume change) in the chamber is recorded with a capacitance manometer. Values for blood flow were calculated from the equation

$$\dot{Q}_c = \frac{\frac{dV}{dt}}{F_{AN} O_2 \times \alpha N_2O};$$

these were instantaneous, continuous, required no blood sampling or catheterization.

This method has now been compared with the direct Fick method for cardiac output in patients catheterized for clinical indications. A special transparent horizontal body plethysmograph was made for this purpose. A double lumen cardiac catheter was inserted to record pulmonary artery and wedge pressure. The lid of the plethysmograph was lowered and vascular pressures recorded simultaneously with the plethysmographic record. Appropriate blood and gas samples were collected for the direct Fick determination immediately before N_2O determinations. Cardiac output in L. per minute in 6 individuals by the 2 methods were as follows: Fick: mean 6.0, S.D. 2.5, S.E. 1.0; plethysmographic N_2O : mean 5.4, S.D. 1.33, S.E. 0.54. The difference was not statistically significant ($p > 0.5$). Reproducibility of paired determinations by the N_2O method were as follows: first run: mean 5.65; second run: mean 5.10. Mean difference 0.55 L. per minute; S.D. 0.94, S.E. 0.37. The second run appeared slightly lower than the first, possibly owing to accumulation of N_2O in the body. When first runs were compared with the direct Fick method, the mean difference, 6.0-5.65, could be explained by the normal degree of right-to-left shunt, about 5 per cent. A comparison between the instantaneous pulse pressure gradient and pulse flow waves has been made.

Fatty Acid Composition of Plasma and Plaque Lipids in Patients Receiving Natural and Purified Polyunsaturated Fats

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It has been well demonstrated that the intake of fats containing polyunsaturated fat, particularly fats rich in linoleic acid, will produce a major decrease in blood lipids. More recently evidence has been presented which suggests that fish oils, rich in a variety of polyunsaturated fatty acids, most of which do not fall in the category of "essential fatty acids," will also lower plasma lipids to a significant degree. These observations have raised a number of questions, foremost of which are: What is the mechanism of the plasma lipid-lowering effect of polyunsaturated fat? Is the lipid-lowering effect of the fat directly proportional to the number of double bonds which it contains, regardless of structure? Are fatty acids which are "essential" for the rat, identical with those which are "essential" for the human?

As an approach to these problems, the plasma lipids and plaque lipids, including esterified cholesterol, total phospholipids, mono-, di-, and triglycerides and unesterified fatty acids, have been fractionated by chromatographic and chemical means. Methyl esters of the fatty acids of each of these compounds have been prepared and quantitative analysis by gas chromatography carried out. To date, the following data have been obtained:

In the normal individual on an average diet, the predominant fatty acid in the cholesterol esters is linoleic acid. The predominant fatty acid in the triglyceride is oleic acid.

The composition of all the plasma lipids, to some degree, reflects the fatty acid composition of ingested or infused fat. The extent of this varies considerably between individuals. Significant differences were observed in many abnormal subjects, as compared with the usual response of the normal individual.

During and following infusion of a safflower oil emulsion, containing large amounts of linoleic acid but no arachidonic acid, arachidonic acid has been found in the unesterified fatty acid fraction of the plasma.

During the ingestion of fish oils containing no arachidonic acid but large amounts of highly unsaturated fatty acids which are not essential (for rats), very significant increases in the amount of arachidonic acid have been observed in the cholesterol esters and, at times, in other fractions.

Plaque lipids vary significantly from plasma lipids, with particular respect to much larger amounts of stearic acids, and of mono- and diglycerides. Plaque lipids vary remarkably in composition in the same individual in different locations.

Interpretation of some of the above findings have been made. Included is a consideration of the question as to whether the human subject (a

compared to the rat) may have the ability to transform "nonessential fatty acids" to arachidonic acid. If this interpretation is correct, one may have reason to place at least some of the fatty acids from fish oils in the "essential" category for humans, and to state that structure of polyunsaturated fatty acids, rather than number of double bonds, per se, determines their ability to lower plasma lipids.

Considerations of Technic in Surgical Repair of Ventricular Septal Defect

John W. Kirklin and James W. DuShane, Rochester, Minn.

Different technics exist for the repair of ventricular septal defect. Exposure within the ventricle can be obtained with the heart in action or arrested. If arrest is employed, potassium, acetylcholine, hypothermia, or anoxia can be employed to induce it. The repair itself can be done with the use of a plastic material, or by direct suture used in one way or another.

Some experience with all these technics has been obtained. For the last 15 months, direct suture has been employed with the heart quieted by the production of asystole. The sutures have been placed in a specific way, designed to minimize the incidence of heart block and to enhance the probability of complete repair.

A review of this experience indicates that the incidence of complete and permanent heart block has been 6 per cent. Although there continue to be uncommon instances of incomplete repair, late disruptions have not been identified.

Detailed data concerning heart block and completeness of repair are available for the entire series. The technic at present in use and the advantages and disadvantages thereof, have been evaluated.

Effects of Acetylcholine on the Isolated Atria of Normal and Dystrophic Mice

Morris Kleinfeld, Bernard Murphy, Maurice Mufson, and Edward Stein, New York, N.Y.

Isolated atria of the normal mouse (strain 129, Jackson laboratory) and of the dystrophic litter mate were suspended in a perfusion chamber and bathed by slowly moving Ringer-Locke's solution into which 95 per cent oxygen and 5 per cent carbon dioxide were bubbled. The temperature of the bath was maintained between 34° and 36°. Transmembrane potentials from the spontaneously beating atria obtained by intracellular microelectrodes were correlated with the isometric tension developed before and after the administration of

acetylcholine ($3.3 \times 10^{-4}M$) as a constant perfusion.

The changes observed with acetylcholine were: 1. Significant slowing of heart rate in both strains, but more marked in the dystrophic strain, even to the point of asystole in approximately 50 per cent contrasted to none in the normal atria. 2. Appreciable increase in the tension output in both strains. After return to Ringer-Locke's solution, the amplitude usually returned to control levels. The tension output of the untreated controls varied between 100 to 150 mg. in the normal strains and 25 to 50 mg. in the dystrophic strains. 3. Acceleration in the rate of repolarization in both groups.

There was no significant change in either group in the magnitude of the action potential or of the resting potential, or in the latter even when asystole occurred.

The smaller isometric tension developed by dystrophic atrial muscle compared to the normal may be related to the smaller cell size and the morbidity of the former. The increased inotropism exhibited by atria of both strains following the administration of acetylcholine is unexplained.

Breath-holding Time in the Evaluation of Organic and Functional Heart Disease

Robert M. Kohn, Buffalo, N.Y.

The degree of cardiac dysfunction in 85 patients referred to the Cardiac Work Evaluation Unit was evaluated by means of general physical examination, a variety of static and exercise tolerance tests, and psychological interviews. Analysis of the data showed that the measurement of breath-holding time provided a useful assay of cardiac status, especially in the differentiation of organic cardiopulmonary disease from functional disorders.

Patients were instructed to inhale deeply, exhale completely, and after a second deep inhalation to hold the breath as long as possible, exhaling at the limit of tolerance. Normal subjects and those with class I cardiovascular disease averaged 48 ± 10 seconds. Patients with class III heart disease averaged 35 ± 9 seconds. Class II cardiovascular disease was a heterogeneous group with considerable scatter, but in general with intermediate values. Patients with pulmonary emphysema without heart failure averaged 23 ± 2 seconds, no case being below 15. Thirteen patients with functional cardiovascular disease, including some with minimal organic findings, averaged 15 ± 6 seconds; only 1 of these patients held the breath for more than 20 seconds. In organic heart disease and emphysema, holding time is shortened because

of reduced cardiopulmonary reserve. In psychogenic disturbances, the holding time is shortened even more, although cardiorespiratory reserve may be normal. These results indicate that breath-holding time assists in the evaluation of the severity of organic cardiovascular disease and in the diagnosis of functional cardiovascular disorders. In general, if the patient is able to walk into the examining room (excludes severe pulmonary disease and class IV cases) inability to hold the breath for at least 20 seconds suggests that symptoms are predominantly on a functional basis.

Artificial Heart in the Chest and use of Polyurethane for Making Hearts, Valves, and Aortas

Willem J. Kolff, Tetsuzo Akutsu, and Harry Norton, Cleveland, Ohio

Our artificial heart in the chest derives its mechanical energy from 5 coordinated solenoids arranged in a rosette. The electric current enters the chest through wires. The energy and the generated heat are transferred via oil to 2 ventricles. The ventricles, valves, atria, and the base of both the aorta and the pulmonary artery are made of Polyurethane VC. The filling of the ventricles is effected by the atrial pressure so that suction is avoided. Systole is effected by the solenoids; both ventricles empty completely. Over a period of time both ventricles pump equal amounts since increased atrial pressure will result in larger filling of the corresponding ventricle. With a rate of 76 and a stroke of 130 msec., each side of the heart pumps 1,500 ml. per minute. A movie has been made showing this artificial heart replacing a dog's heart. Cinecardioangiography visualizes the circulation. The dog lived for 3 hours and 20 minutes. It breathed on its own and sustained satisfactory circulation.

The heart valves can also be used separately to replace natural heart valves. Valves were inserted in the hearts of 51 dogs. Recently, an artificial mitral valve functioned well for 5 weeks. Fibrous tissue grew into the polyurethane sponge surrounding the valve and fixed it firmly in the dog's heart. A cinecardioangiogram demonstrating its function has been made.

Thrombus formation: so far, 9 smooth grafts in the aorta all thrombosed, whereas 13 of the 16 sponge grafts remained open for 6 months.

Lipoproteins Quantitated by Paper Electrophoresis as an Index of Atherosclerosis

Robert J. Kositchek, Beverly Hills, Calif., Reuben Straus, and Moses Wurm, Burbank, Calif.

Data dealing with cholesterol, phospholipid, cholesterol/phospholipid ratios, and total lipids

in a large group of "normal" and manifest coronary artery disease patients have been evaluated. These have been found to have a low order of significance in determining the atherosclerotic status for both individuals and for groups.

A new procedure for separating five lipid-containing fractions of serum by paper electrophoresis and a method of quantitation has been reported from our laboratory. All lipoproteins fractionated by paper electrophoresis and visualized with Fat Red 7 B, except the γ -lipoprotein plus neutral fat fraction, reveal considerably more significant information relative to atherosclerosis than any of the chemical studies.

Our findings with respect to the β -lipoproteins reveal that groups of normals may be differentiated from coronary atherosclerotics, since the difference in the mean values for each is highly significant ($t = 4.88$). It appears possible to identify the atherosclerotic status of an individual with absolute certainty if the lipalbumin concentration is below 10.4 per cent or above 21.5 per cent. The calculated Fisher's t of 5.78 also indicates that the difference in the mean for the 2 groups is highly significant.

Using the beta/lipalbumin ratio, one third of the population can be correctly classified, without chance of error, when this variable is below 2.56 or greater than 6.82. On the other hand, if an 80 per cent level of confidence is acceptable, more than half of the population can be diagnosed when values are less than 2.97 or more than 5.12.

Hemodynamic Effects of Closed Chest Extracorporeal Circulation in Experimental Myocardial Infarction with Shock

Leslie A. Kuhn, Frank L. Gruber, Albert Frankel, and Sherman Kupfer, New York, N.Y.

The ability to raise coronary perfusion pressure and other hemodynamic effects of extracorporeal circulatory support were investigated in closed chest dogs with shock following plastic sphere coronary embolization, normal dogs, and those with ventricular fibrillation.

In animals with prolonged ventricular fibrillation and no cardiac output, 60 cc. per Kg. per minute pumped from the vena cavae into the abdominal aorta produced coronary perfusion adequate to permit defibrillation. However, when a cardiac output was present, in dogs with hypotension following coronary embolization or in normal dogs, similar shunting of blood failed to raise central aortic pressure.

To raise central aortic pressure in these animals it was necessary to increase vascular resistance. This was accomplished by inflating a balloon catheter inserted via a femoral artery into the abdomi-

nal aorta. Blood pumped from the superior vena cava supplied the distal aorta. In normal animals, maintained for 4 hours with this method, proximal aortic pressure rose appreciably. Distal aortic mean pressure averaged 86 mm. Hg. Coronary flow increased. Cardiac output and left ventricular work diminished due to shunting part of the venous return into the distal aorta.

In animals with shock following coronary embolization, similar results were obtained, mean central aortic pressure rising from 73 to 150 mm. Hg.

It is concluded that conventional techniques, employing shunting from the veins to the abdominal aorta, are ineffective in raising coronary perfusion pressure unless there is severe congestive heart failure or no cardiac output. To raise aortic pressure by mechanical means in experimental myocardial infarction with shock, it is necessary to increase vascular resistance.

Alterations of Myocardial Blood Flow and Oxygen Consumption and of Pulmonary Gaseous Exchange by Lipemia

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To investigate the mechanism of lipemia-induced myocardial ischemia, the effects of lipemia upon coronary blood flow (nitrous oxide method) and myocardial oxygen consumption, and upon arterial oxygen saturation and CO₂ content, were determined in 19 dogs with myocardial scars and in 11 control dogs. Lipemia was induced by infusion of either postprandial lipemic plasma from a donor dog (rendered nephrotic or hypoalbuminemic) or a commercial fat emulsion.

Mean coronary blood flow and myocardial oxygen consumption of dogs with myocardial scars were 84.83 ml. and 8.91 ml. per 100 Gm. of left ventricle per minute respectively, with mean myocardial oxygen extraction of 10.63 volumes per cent, before lipemia. During lipemia, mean coronary blood flow and myocardial oxygen consumption were 69.73 ml., a 17.8 per cent decrease ($p = < .001$), and 7.18 ml., a 19.5 per cent decrease ($p = < .001$), per 100 Gm. of left ventricle per minute respectively, with mean myocardial oxygen extraction of 10.55 volumes per cent. These physiologic parameters were not significantly altered with glucose or fat-free emulsion base infusions. In the control dogs, similar but less marked decreases of coronary blood flow and myocardial oxygen consumption were observed during lipemia.

The concomitant decrease in coronary blood flow and myocardial oxygen extraction with no significant change in R.Q. and mean arterial blood

pressure suggests an impediment to oxygen diffusion during lipemia. The 2.7 per cent drop in mean arterial oxygen saturation suggests that lipemia interferes with pulmonary oxygen diffusion. Hyperventilation lowered CO₂ content. The data indicate that lipemia can reduce myocardial oxygen availability.

Diagnosis and Surgical Treatment of a Type of Triatrial Heart

Conrad R. Lam, Robert F. Ziegler, Ellet H. Drake, and Edward Green, Detroit, Mich.

Five patients have been observed in whom the diagnosis of a peculiar type of triatrial heart has been established. There are 2 left atria and 1 right atrium. The left atria communicate with the right by separate atrial septal defects. One of the left atria receives the pulmonary veins, while the mitral valve is at the lower part of the other left atrium. Obviously, closure of either of the septal defects would result in a complete block of the circulation. Surgical correction consists of the removal of the septum between the two left atria and closure of the resulting large interatrial communication. The operation was carried out in all 5 cases. Two adults were operated on under hypothermia, with 1 survival; the cause of death in the fatal case was excessive pulmonary resistance, which was the result of long-standing pulmonary hypertension. Three infants were operated on with the pump-oxygenator. One is well and 2 expired in the immediate postoperative period of pulmonary complications.

The diagnosis was established preoperatively in 3 patients. This anatomic situation should be suspected when cardiac catheterization gives the characteristic findings of uncomplicated interatrial septal defect, but the peripheral blood shows unsaturation. Confirmation may be obtained by angiocardiology.

Surgical Treatment of Aortic Stenosis

Conrad R. Lam and Rodman E. Taber, Detroit, Mich.

One hundred and seven operations for acquired and congenital aortic stenosis were performed. Aortic stenosis is a difficult disease to treat, but it is our conviction that real progress has been made in surgery. We continue to use the original transventricular operation in selected cases, particularly in patients in the older age group. The last 2 patients were 65 and 67 years old, and an excellent immediate result was obtained in each. Of the total group of 52 patients operated on by this method, 16 have died. The closed method,

with the tunnel sutured to the aorta, was abandoned after 5 deaths in 14 cases and several recurrences in the cases which survived operation.

Direct vision commissurotomy is being used with increasing frequency. Nine patients with acquired aortic stenosis were operated on with the adjunct of hypothermia; irreversible ventricular fibrillation was the cause of death in the 3 patients who did not survive. The pump-oxygenator has been used in 16 cases; 3 of these with severe calcific deformity of the valve did not recover.

Congenital aortic stenosis must be dealt with by direct vision. Hypothermia was used in 14 cases with only 1 death. However, we prefer the use of the pump-oxygenator; and in the last 5 consecutive cases, excellent results have been obtained.

Retrograde Arterial Catheterization of the Left Heart: Experience with 117 Infants and Children

Edward C. Lambert and Peter Vlad, Buffalo, N.Y.

One hundred and seventeen patients with congenital cardiovascular defects were studied by retrograde arterial catheterization of the left heart in conjunction with conventional right heart catheterization. The ages of the patients ranged from 3 weeks to 20 years. Forty-three patients, or 27 per cent of them, were infants.

The procedure was successful in 105, or 90 per cent of the cases. Five of the 12 failures appeared to be due to aortic stenosis. However, it was possible to enter the left ventricle in 6 other cases of aortic stenosis and thus locate the site of the obstruction. The left atrium was entered in 21 of the 41 instances when an attempt was made to direct the catheter into this chamber.

Diagnostically, this procedure proved to be of special value in that it allowed: (1) simultaneous pressure determinations on both sides of valves and septa; (2) multiple dye dilution curve determinations across the cardiac septa and valves; (3) selective angiocardiology of the left heart and aorta. Such angiocardiology proved to be peculiarly suited to the demonstration of mitral regurgitation and ventricular septal defects in the 41 instances in which this procedure was performed.

A final advantage of this combined catheterization method is that with little added effort and hazard it allowed for a marked degree of versatility. In this series, it made possible the detection of complicating anomalies in 26 cases. (In these instances, right heart catheterization had failed to demonstrate them.)

The safety of this approach was indicated by the lack of evidence of damage to the valves or

endocardium in the 15 hearts subsequently examined at autopsy. One death might be ascribed to the procedure inasmuch as the thrombosis of the renal artery was found at autopsy, 5 days following the test.

Clinical Assessment of Mitral and Aortic Regurgitation by the Use of Multiple Indicator-Dilution Curves

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In contrast to a reasonably accurate quantitation of valvular stenosis of the heart, assessment of regurgitation is still difficult. The analysis of pressure tracings or the evaluation of single indicator-dilution curves has not always been reliable, particularly in the absence of heart failure. When injected into a peripheral vein, mixing of an indicator substance is essentially completed by the time tinged blood leaves the right ventricle; such curves are not appreciably altered by further passage through the central circulation (lungs and left heart). Using the Wood oximeter, an indicator-dilution curve obtained from the pulmonary artery (PA) is therefore grossly similar to a simultaneously recorded curve sampled from a free-flowing femoral artery (FA). The presence of congestive failure or cardiac enlargement will influence both curves equally. In regurgitation, occurring at the mitral or aortic valve, the left heart curve (FA) is modified, while the former (PA) remains unchanged. Differential changes of certain curve parameters, particularly the differences in the appearance times and the mean circulation times of the 2 curves, bear a quantitative relationship to the ratio of forward flow (measured by direct Fick principle or dye curves) to total flow, which is the sum of forward and regurgitant flow. This permits estimation of the amount of blood regurgitated as a fraction of the total moving through the heart and lungs. Certain internal checks, cases of patent ductus arteriosus and estimation at surgery, have supported the clinical usefulness of such an approach, and metered regurgitation in hydraulic models and in dogs have confirmed the data obtained in human subjects.

Irrespective of the theoretical basis, this has provided a useful clinical technique for a semi-quantitative assessment of left ventricular regurgitation and, in certain instances, has allowed a separation of aortic from mitral insufficiency. This can be demonstrated by pertinent clinical examples of mild, moderate, and severe regurgitation in the presence or absence of heart failure, and in the face of normal or abnormal single dilution curves.

Interrelationships Between Renin and Electrolytes

Herbert G. Langford and Sue Cotten, Jackson, Miss.

Recent reports of a reciprocal relationship between renin content of the kidney and sodium load suggested that the acute effects of renin upon serum electrolytes should be examined. The effects of saline-DCA pretreatment upon these responses were also studied.

Mongrel dogs anesthetized with pentobarbital were used. Blood was withdrawn for Na and K determination before and at 30 second intervals for 5 minutes after the injection of 40 Goldblatt units renin. Samples were also taken at 10 and 15 minutes. Five dogs were then given 5 mg. DCA daily for 3-7 days, plus 1 per cent NaCl water; then the above was repeated. Serum potassium rose 1.4 mEq. per L. (range 0.3-4.6). While there was considerable variation in amount of rise, the rise was consistent, and usually reached its peak 2-3 minutes after the blood pressure peak. Serum sodium fluctuated wildly for the first 2-3 minutes, then usually fell. (Mean fall 9.9 mEq., range +7, -17, N = 9).

In the animals pretreated with DCA and saline, the peak blood pressure response was significantly increased, from 70.4 mm. Hg increase before DCA to 94.8 mm. Hg increase afterwards, $p = 0.01$. The rise in serum K was abolished in 2 of these animals despite the marked pressor response.

In contradistinction to previous reports, DCA does sensitize the dog to the pressor response to renin. The zona glomerulosa enlargement reported after renin administration may be related to the marked electrolyte changes noted here. The possibility that these changes are due to epinephrine release is under study.

Aldosterone Secretion and Arterial Hypertension

John H. Laragh, Stanley Ulick, W. Januszewicz, Quentin B. Deming, William G. Kelly, and Seymour Lieberman, New York, N.Y.

The role of aldosterone in human arterial hypertension has not been elucidated. Previous studies involving the measurement of the small amounts of aldosterone present in urine have yielded equivocal results possibly because these levels may not reflect significant changes in adrenal secretion.

The present study was designed to investigate the amount of aldosterone actually secreted by the adrenals. Utilizing an isotope-dilution technique, levels of the aldosterone secretion have been studied in relation to changes in sodium intake, acid-base balance and, when possible, adrenal morphology.

Ten patients with benign essential hypertension, 5 with advanced hypertension, and 12 with malignant hypertension have been studied. The

results have been compared to those obtained in normal patients, in patients with unilateral renal disease, and in 5 cases of primary aldosteronism.

It was found that aldosterone secretion was uniformly within normal limits (175-330 γ per day) in benign essential hypertension. In patients with renal or vascular complications, the secretion may be significantly increased (450-1,690 γ per day). However, in 11 of 12 patients with malignant hypertension, the secretion of the hormone was uniformly, and often markedly, increased to 520-2,750 γ per day.

It thus appears that aldosterone plays an important role in the syndrome of malignant hypertension. However, it is not clear whether the hypersecretion is the cause of or the response to the diseased state. Whether aldosterone is an etiologic factor in humans, as are the mineralocorticoids in experimental animals, is not established by these findings.

Electrocardiographic Pattern Consisting of Pronounced U Wave Inversion with Slight RS-T Segment Changes Seen in Severe Acute Myocardial Ischemia

Richard Lasser, Frank L. Gruber, and Stanley R. Robbin, New York, N. Y.

A distinctive electrocardiographic pattern, characterized by marked inversion of the U wave, accompanied by only slight depression of the RS-T segment, is being presented as an initial change occurring in myocardial ischemia of sufficient severity so as to be a premonitory sign of myocardial necrosis. Minimal alterations of the T wave may or may not be present.

Three cases are shown in which the initial electrocardiogram illustrated these characteristic findings. In 2 patients, serial electrocardiograms showed the usual development of myocardial infarction, while the third patient developed ventricular fibrillation immediately after the first tracing was taken and expired. In the 2 patients who subsequently showed the electrocardiographic evidence of myocardial infarction, the infarction occurred in the area which had the deepest inversion of the U waves.

The importance of this pattern lies in recognizing its temporal relation to acute myocardial ischemia and necrosis, it apparently being an initial ischemic change. Though the depressions of the RS-T segments are minimal, the definite inversion of the U wave, which is never seen in normal records, confirms the diagnosis of severe acute myocardial ischemia.

Complete Heart Block as a Complication of Repair of Ventricular Septal Defect in Children

Ronald M. Lauer, Patrick A. Ongley, James W. DuShane, and John W. Kirklin, Rochester, Minn.

Our experience with complete heart block complicating open heart surgery for ventricular septal defect, alone, or in combination with valvular or infundibular pulmonic stenosis, indicates 48 instances of heart block in the 298 children from 2½ months to 15 years of age who were operated on. Block occurred in 33 of the 174 children operated on for ventricular septal defect alone and in 15 of the 124 children operated on for ventricular septal defect with pulmonic stenosis.

Eighteen patients died, the rhythm returned to normal in 18 and complete block continued in 12. The incidence of permanent heart block (at death or discharge) was 5.2 per cent with the beating heart, greater with asystole, using either prosthetic closure or direct suture of the ventricular defect (16 per cent), and again less with introduction of a suture technic devised specifically to avoid the conduction system (5.5 per cent).

A study of the incidence of block and fate of the patients has been made. The incidence of block in relation to the ratio of pulmonary artery to systemic artery pressure in ventricular septal defects showed a relatively greater incidence of block among patients with higher ratios with each of the surgical methods. The approximately equal percentages of patients who had high pulmonary arterial pressures treated by each of the 3 surgical methods show the similarity of selection of cases for operation.

Effect of Prolonged Chlorothiazide Therapy on Body Fluids and Electrolytes

Philip L. Lauwers and James Conway, Ann Arbor, Mich.*

Body fluids and body sodium have been investigated in hypertensive patients on 1 Gm. chlorothiazide daily for a period of 24 to 60 days. In contrast to the findings after a few days of treatment, the blood and extracellular fluid volumes are at approximately normal levels after 1 month or more on the drug. The initial fall in body weight persists over this period and is reflected in a reduction in total body fluid volume (antipyrine space). These findings taken together indicate that the prolonged effect of chlorothiazide is chiefly manifested in a depletion of the intracellular fluid volume. Exchangeable sodium in mEq. per Kg. of body weight is not decreased and sometimes is increased.

Similar findings are obtained both in subjects showing a reduction in blood pressure when on chlorothiazide and in those whose blood pressure remains unchanged. However, a fall in blood pressure does not occur without a fall in body weight.

Since we have shown that the prolonged blood pressure reducing properties of chlorothiazide are

not due to changes in cardiac output, it seems possible that body fluid depletion causes a reduction in peripheral resistance. The site of loss of fluid which is important for the lowering of the blood pressure has, however, to be determined.

Pharmacologic Therapy of Hypertensive Vascular Disease, and Freedom from "Strokes": A Preliminary Report

Richard E. Lee, Arthur W. Seligmann, Melvin Clark, and Vincent DuVigneaud, Jr., New York, N.Y.

Within the past 6 years, 7 of our patients with hypertensive disease have had a total of 9 "strokes." Each patient had hypertensive vascular disease, grade I-II, without known cardiac or renal involvement. Their ages were from 28-77 years. All of the "strokes" took place while the patients were not receiving antihypertensive drugs. In 6 subjects, these happened during close follow-up, 1 prior to beginning therapy and the remaining 5 within 2-9 weeks after stopping medication. Moreover, they all occurred in the group of 31 patients (total of 187 on follow-up) who had either not been treated with, or who had completely discontinued drug therapy. The remainder (156 cases) have thus far been free of cerebral-vascular accidents. In 4 patients, where blood pressure was measured closely before and after stopping treatment, the CVA was accompanied by a rise in blood pressure to severely increased levels. Analysis of the data by correlation techniques and by χ^2 indicates the association between stopping medications and subsequent "stroke" is very likely significant ($p < 0.01$). Continued drug therapy of at least certain hypertensive patients seems, therefore, consistent with continued well being, but its interruption may be followed by a cerebral-vascular accident.

Use of an Artificial Pacemaker for Acetylcholine-Induced Cardiac Arrest during Coronary Arteriography

William M. Lemmon, J. Stauffer Lehman, Victor Kimel, and Charles P. Bailey, Philadelphia, Pa.

The selection of patients for direct coronary artery surgery may depend, in large measure, upon preoperative demonstration of intracoronary artery pathology. Reliable contrast visualization of the major coronary arterial tree requires an adequate perfusing force acting upon a satisfactory concentration of radiopaque medium for a short period of time. Such factors as heart rate, stroke volume, length of injection time and dilution of a given quantity of injected radiopaque material may vary so widely from patient to patient as to produce great variation in opacification of the

coronary arterial system. To eliminate some of these variables, we have resorted to inducing cardiac arrest immediately before injection of the opaque material.

A short period of cessation of cardiac motion assists in obtaining clear and detailed radiographic demonstration of the opacified coronary arteries, and it appears that there is improved coronary arterial opacification during the diastolic arrest. Such induced cardiac arrest may be induced by placing 5 to 8 mg. of acetylcholine into the connecting tubing of the injection catheter system immediately preceding the radiopaque agent. The entire mass is injected, in 2 seconds or less, through a catheter introduced by way of a peripheral artery and positioned with its tip at the level of the aortic sinuses.

The period of cardiac arrest produced by the acetylcholine is somewhat unpredictable and if longer than 8 to 10 seconds may lead to cerebral hypoxia and convulsive seizure. To prevent such a complication, we have arbitrarily limited the period of arrest to 8 seconds by use of an artificial pacemaker, which is activated if the arrest extends to 8 seconds.

In our hands, this procedure of coronary arteriography has appeared to be relatively safe and reliable with a very low morbidity and no mortality. The quality of the resulting coronary arteriograms has shown significant improvement over that obtained by other methods we have employed.

Accurate Technic for the Volumetric Calibration of Dye-Dilution Curves

Susan C. Lenkei, Toronto, Canada, Samuel M. Fox, III, Thomas N. Lynn; and with the technical assistance of Maurice W. Moore, Bethesda, Md.

Numerous errors in calibration can destroy the value of quantitative dye-dilution flow determinations. The commonly used secondary standard (spectrophotometry) is inconvenient and dependent upon plasma extraction and hematocrit corrections influenced by hemolysis. The following procedure avoids these.

The blood drawn during the inscription of the curve is divided volumetrically into flasks. Given volumes of the same dye as injected into the patient are introduced into all but 1 of the flasks from a micrometer syringe. This results in known different concentrations. This blood is run through the same densitometer forming deflections for comparative measurements.

The following formula relates the differences in dye concentration to recorded deflections:

$$\frac{\text{Micrometer syringe dye introduced (ml.)}}{\text{Blood and dye in flask (L.)} \times \text{Deflection (mm.)}} = \text{Factor (ml./L./mm.)}$$

This factor is introduced into the standard indicator dilution formula:

$$\text{Blood Flow (L./min.)} = \frac{\text{Dye injected into patient (ml.)}}{\frac{\text{Summated area of primary curve}}{\text{Intervals/min.}}} \times \text{Factor (ml./L./mm.)}$$

The advantages of the method are: (1) no secondary reference technic required; (2) independence from hematocrit and hemolytic effects; (3) applicability to all dyes irrespective of concentration; (4) no additional blood required; (5) calibration subject to prompt inspection for validity, and repeated checking is easy if linearly responsive instrument is used; (6) same calibration factor can serve for rapidly successive flow curves. Insignificant change in this factor occurs even with many changes in the blood constituents.

Pathology of the Conduction System in Acquired Heart Disease: II. Complete Right Bundle-Branch Block

Maurice Lev, Chicago, Ill., Paul N. Unger, Milton E. Lesser, Miami Beach, Fla., and Alfred Pick, Chicago, Ill.

This work is part of a long-term study of the anatomic base of electrocardiographic abnormalities.

The hearts of 8 patients with the electrocardiographic abnormalities characteristic of complete right bundle-branch block (QRS 0.12 sec. or more) were studied histopathologically by a method previously described by Lev and MacMillan. By this method, the S-A node, the approaches to the S-A and A-V nodes, the A-V node, the A-V bundle, the bundle branches, and the entire atria and ventricles are sectioned and studied semiquantitatively. The findings in these hearts were compared with the findings in 1 heart with advanced A-V block with an idioventricular pacemaker, revealing the contour of RBBB, and another heart which showed incomplete LBBB earlier, and complete RBBB later. Nine hearts were the seat of arteriosclerotic disease, and 1 of myocarditis.

There was an excellent correlation between old lesions in the bundle branches in the 8 cases revealing RBBB. Here the right bundle branch was moderately or severely fibrosed, or completely scarified, while the left bundle branch showed only mild or no changes. Where recent lesions had to be correlated with RBBB, both bundle branches were evenly involved, or the right sometimes more than the left. In the case with previous incomplete LBBB followed by complete RBBB, old and recent lesions were found in both bundle branches. In the case of advanced atrioventricular block, there was an old lesion only in the right bundle branch, with severe acute lesions in both bundle branches.

Late Peaking of the T Wave as a Digitalis Effect

Harold D. Levine, Evangelos T. Angelakos, and Bernard Lown, Boston, Mass.

In 200 consecutive electrocardiograms, showing "digitalis effect" (hammock-shaped RS-T, shortened Q-T, inverted T-100 recorded in 1949 and 100 in 1958), 22 showed terminal T-wave peaking. In 11, renal disease or potassium supplementation may have contributed to the T wave change. In the remaining 11, no hyperkalemia or electrolyte imbalance existed. Digitalis appeared to be the probable cause of the late T wave peaking.

In 100 digitalizations in dogs to an endpoint of ventricular tachycardia, similar late peaking was found 42 times. In 18, the T waves showed a similar late spiked contour but were inverted. In 40, no such changes occurred. The T wave alterations were noted early in digitalization, when 30 to 60 per cent of the toxic dose had been administered.

The animals which exhibited T wave changes irrespective of direction, had a rise in serum potassium of about 0.6 mEq./L. during digitalization. Those without T wave change had a potassium shift of only 0.31 mEq./L. Generally, even after the potassium shift, the values were within the normal range.

Raising the serum potassium level in the dog to 6.0 mEq./L. by infusion does not generally result in spiked T waves. Digitalization seldom increases the serum potassium concentration to this level. It follows that the T wave changes are not due to alteration of this cation in the extravascular compartment. Since digitalis may induce a loss of cellular potassium, the hyperkalemic pattern may be due to the transcellular potassium gradient.

Large-Screen Cycloidal Vectorcardiography

David C. Levinson, Herbert Shubin, and Louis G. Fields, Los Angeles, Calif.

Equipment has been developed for high resolution vectorecardiography. This consists of a 17 inch oscilloscopic screen with specially developed amplifiers, and an 8 channel electronic switch. This equipment affords simultaneous visual display and permanent recording of 3 vector planes, plus a timing electrocardiogram. The vectors and electrocardiogram may be stationary or cycloidally (sliding) in either a horizontal or vertical direction when viewed.

A single QRS vector loop can be magnified with fidelity to fill the entire 17 inch screen. The P and T waves are correspondingly enlarged and are clearly visualized as to magnitude, direction and timing. Extremely low noise levels enhance these large displays. The vectors are timed to 0.0006

seconds and in addition to 0.004 seconds in any given loop.

Appropriate clinical illustrations demonstrate the advantages of the above developments.

Disclosure of a Second Blood Protease by Differential Chloroform Treatment of Serum

Jack Lieberman, Torrance, Calif.

The activation of blood plasminogen by shaking serum with chloroform is an established technique. Recently, we discovered that a second proteolytic enzyme can be disclosed by the mere exposure of serum to chloroform and found that shaking with chloroform destroyed its demonstrable activity. This new enzyme differs from plasmin in optimum pH, temperature sensitivity, length of time necessary for activity to appear following chloroform treatment, and activity after filtration through a Seitz filter.

Activation of the second blood protease is effected by adding 1 part chloroform to 5 parts of serum and inverting 5 times in a test tube. The mixture is placed in a 37 C. water bath and sampled periodically. Activity is measured by a caseinolytic method. This "invert" method of chloroform treatment produces a peak of proteolytic activity within 12 to 48 hours, which gradually declines over a period of 14 to 28 days. The optimum pH lies between 6.0 and 6.5. Prior filtration of the serum through a Seitz filter completely prevents the development of activity.

In contrast, the usual "shake" method of chloroform treatment at room temperature results in a peak of protease activity in 14 to 21 days with an optimum pH between 7.0 and 7.5. Prior filtration through a Seitz filter does not affect enzyme activity. When the chloroform-shake-treated serum is initially placed in a 37 C. water bath heat lability is evinced in that no proteolytic activity appears, and the total available activity, as measured by streptokinase activation, rapidly declines. Activity is also quickly lost when the preactivated serum is placed at 37 C.

When serum is treated by the chloroform-invert technique and incubated at 25 C., a combination of the 2 curves of activation results. The optimum pH then ranges between 6.0 and 7.5, apparently reflecting the combination of 2 enzymes.

It is concluded from this study that at least 2 proteolytic enzymes exist in serum.

Critical Role of First Stage Coagulation Factors in Determining Effectiveness of Coumarin Therapy

William Likoff, Seymour Gollub, and Alex Ulin, Philadelphia, Pa.

The prothrombin time test can prove a seriously misleading guide when coumarin drugs are used

or anticoagulation. Recent extensions in the understanding of the effect of prothrombinopenic agents upon the mechanism of intravascular clotting appear to offer an explanation for the inadequacy and a means of avoiding it.

In addition to their effect upon the second stage of coagulation, coumarin drugs are believed to have a profound influence upon factor 9, factor 10, and the Stuart factor. These are regarded as components of the first stage of coagulation. They may be adequately assayed by the thromboplastin generation time.

The present study, based on an investigation of patients treated for myocardial infarction, indicates that the effect of the coumarin drugs on these interrelated first stage factors varies in time and extent and does not necessarily parallel the influence on the second stage. The following types of response have been observed when the second stage coagulation was adequately depressed according to prothrombin time determinations: (1) parallelism between the first and second stages (effectual anticoagulation); (2) nonparallelism (ineffectual anticoagulation); (3) unpredictable escapes from parallelism (ineffectual anticoagulation).

If the clinical effectiveness of prothrombinopenic agents depends upon a parallel response in both stages of anticoagulation, the combined use of the thromboplastin generation and prothrombin times may be mandatory in evaluating patients. The present inquiry into the subject matter also suggests that although nonparallel response and unpredictable escapes occur less frequently than parallel responses, they may contribute to the acknowledged failures of coumarin therapy.

Plasma Flow in Renal Medulla

Lawrence S. Lilienfeld,[†] Mark H. Bauer, and Herman C. Maganzini, Washington, D.C.

Recent investigations have focused attention on the renal medulla as the area in which urine is finally concentrated. The maintenance of hyperosmolarity in this region may be related to the rate of its plasma perfusion. A method has been devised which permits quantitation of plasma flow in the inner medulla. This has been applied to the study of a series of 15 dogs producing hypertonic urine.

131 I-albumin is infused into the ascending aorta of an anesthetized dog via a polyethylene catheter. Arterial blood is continuously collected from a femoral artery during the infusion. Fifteen seconds from the start of the infusion, both kidney pedicles are suddenly ligated. The kidneys are removed and frozen rapidly and sections of renal medulla are weighed and analyzed for radioactivity. Radioactivity of the tissue is related to radioactivity of the arterial blood. Previous studies

have revealed that the incorporation rate of albumin is linear in the papilla during the first minute of perfusion.

Results. One hundred grams of renal papilla in dogs producing hypertonic urine is perfused with albumin at a rate equivalent to 20 ml. of arterial plasma per minute. The inner half of the medulla (adjacent to the papilla) is perfused at a rate equivalent to about 50 ml. of plasma per minute per 100 Gm. of tissue. Assuming that the inner medulla is 10 per cent of the kidney and the papilla 5 per cent, these areas are perfused with plasma at a rate comparable to urine flow through Henle's loops.

Effect of Positive Pressure Breathing on the Pulmonary Circulation

Leonard M. Linde, Daniel H. Simmons, Joseph H. Miller, and Edward L. Ellman, Los Angeles, Calif.

Previous work, indicating that positive pressure breathing has no direct effect on pulmonary hemodynamics, was based on data on the isolated lung or on incomplete data on intact animals. The present study was intended to investigate this problem more fully in the intact animal.

Eight dogs of 8 to 24 Kg. were anesthetized with sodium pentobarbital. Measurements were made during spontaneous and positive pressure breathing on 100 per cent O_2 with a Starling pump set to produce the same tidal volume and respiratory rate. Cardiac output was determined in duplicate by the dye-dilution technic, using indocyanine green. The pulmonary vascular pressure gradient was determined through cardiac catheters in the pulmonary artery and left atrium, using a differential pressure transducer. Effective distending pressures of the artery and vein were similarly determined against intrapleural pressure.

On starting positive pressure breathing, mean cardiac output dropped significantly from 97 to 79 ml. per minute per Kg., a response previously reported and presumably due to increased intrathoracic pressure. Mean pulmonary vascular pressure gradient also dropped from 11.0 to 8.7 cm. H_2O . As a result, there was only a minimal decrease in pulmonary vascular resistance from 117 to 113 units. While absolute pressures in both pulmonary artery and left atrium rose, their effective distending pressures did not change significantly (19.8 to 18.1 and 7.6 to 11.6). These data indicate that positive pressure breathing under these conditions has no significant influence on pulmonary hemodynamics other than the decreased cardiac output, which has relatively little influence on pulmonary vascular resistance in contrast to the known effect of increased cardiac output.

Inhibition of Cholesterol Synthesis, Using MER-29

Philip Lisan, Wilbur Oaks, and John H. Moyer, Philadelphia, Pa.

MER-29, a drug which inhibits cholesterol synthesis, was administered to 36 patients. By virtue of its enzymatic inhibitory action on liver synthesis of cholesterol, the drug produced a statistically significant depression in the serum cholesterol concentration in 32 of the 36 patients. This drop in the cholesterol levels was sustained during the entire 8-month study in all the patients. The mean maximum cholesterol depression was 58 mg. per cent. The drug was well tolerated in the dosage levels used and was relatively free from toxic side effects. It is concluded that MER-29 is an effective drug for lowering serum cholesterol and is being investigated further in regard to its over-all effects on fat metabolism.

Electrocardiographic Changes and Clinical Significance of Atrial Infarction

Chi Kong Liu, Gilbert Greenspan, and Frederick Kellogg, Torrance, Calif.

The first ante mortem electrocardiographic diagnosis of atrial infarction was made in 1948 by Hellerstein. The diagnostic electrocardiographic changes in precordial and unipolar limb leads have not been described.

Clinical diagnosis of atrial infarction was made in 12 cases based on the changes in the 12 lead electrocardiogram over a period of 8 months. Five of the 12 patients died from 4 hours to 4 weeks after the clinical diagnosis was made. At autopsy, 4 had atrial infarction associated with ventricular infarction. One had atrial hemorrhage and chronic myocarditis. Right atrial infarction with mural thrombi was encountered in 1 patient dying of pulmonary infarction without characteristic electrocardiographic changes.

The electrocardiographic changes of the cases proved at autopsy are:

Change of the P-Ta segments. In the precordial leads, elevation of the P-Ta in V_{4-6} with reciprocal depression of the same segment in right precordial leads V_{1-3} were observed in 4 patients. In 1 of the patients, the P-Ta change was observed in precordial leads but not in standard leads. The characteristic P-Ta changes, suggestive of atrial injury current, had almost disappeared the next day in 2 instances. Elevation of P-Ta in Leads I, aVL and depression of the same segment in 2, 3 and aVF were observed in 3 cases.

Supraventricular arrhythmia. Atrial premature beats, atrial tachycardia, supraventricular tachycardia, wandering pacemaker, atrial fibrillation, and nodal premature beats.

Atrial infarction is clinically significant because of the frequent association with supraventricular arrhythmias, mural thrombus formation and pulmonary and peripheral embolism.

Myocardial Myosins

Rose E. London and Anwar A. Hakim, Miami, Fla.

In order to study the physiologic factors which influence the physicochemical properties of myosin A (myosin) and myosin B (actomyosin) of human cardiac muscle, we were led to study the change in the myosins from time of death until the time of autopsy in animals.

Myosin A and myosin B have been prepared from the cardiac muscle of dogs. The cardiac muscle was obtained from living dogs while under anesthesia and from animals 5 hours after death; it was frozen directly in dry ice after removal from the animals. Myosin A was extracted, using 0.5 MKCl and 0.1 M potassium phosphate buffer of pH 6.5 and purified according to techniques of Szent-Györgi, while myosin B was extracted by the procedure of Mihayli, Laki and Knoller.

Ultraviolet spectrophotometric analysis of the 2 myocardial preparations, using model DU Beckman spectrophotometer, showed characteristic spectra containing a maximum at wave length 260 $m\mu$. The presence of nucleic acid in these preparations has been confirmed by chemical and enzymic analysis. Ribonuclease or deoxyribonuclease action on either myosin A or myosin B was followed by paper chromatography and showed that both preparations contained ATP and nucleic acids.

Myocardial myosins A with actin in the presence of ATP resulted in a precipitate which was analyzed and compared with myosin B. The formation of the precipitate with increasing concentrations of myosin A, actin and/or ATP was studied.

The presence of nucleic acids in the most purified preparations of myocardial myosin contributes additional information regarding the function of endogeneous adenosinetriphosphate in the transfer of energy to the myocardial contraction mechanisms. Effect of possible alterations in either the stricture of the ratios of the myosins or the nucleic acids on the myocardial contraction will be discussed.

Detection and Localization of Cardiac Shunts with Injections of Kr^{85} Solution

Robert T. L. Long, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

Following injection of krypton in solution into the right side of the heart, approximately 95 per cent is cleared during 1 passage through the pul-

monary circulation. Arterial blood activity is low when radioactive krypton (Kr^{85}) is injected in the absence of, or distal to the origin of a right-to-left shunt. However, when injected proximal to the origin of such a shunt, a fraction of the Kr^{85} bypasses the pulmonary capillary bed and appears in arterial blood. Thirty to 50 μc . Kr^{85} was injected into the right heart and arterial blood was sampled during the next 15 seconds. In 19 patients without right-to-left shunts, the activity per milliliter of arterial blood was always less than 9.0×10^{-5} and averaged $2.5 \pm 2.6 \times 10^{-5}$ of the total radioactivity injected. In 8 patients with proved small right-to-left shunts, the radioactivity per milliliter of arterial blood always exceeded 8.2×10^{-5} and averaged $23.7 \pm 12.2 \times 10^{-5}$ of the total activity injected.

Following injection into the left heart proximal to the origin of a left-to-right shunt, Kr^{85} promptly arrives in the pulmonary vascular bed and immediately appears in the expired gas where it may be readily detected. In 22 such patients, Kr^{85} appeared in the expired gas in an average of 4.0 ± 1.6 seconds. However, after injection distal to the origin of a left-to-right shunt in 18 patients, the appearance of Kr^{85} in the expired gas was delayed to a mean 15.0 ± 5.0 seconds. The techniques described are simple to apply and sufficiently sensitive to detect and localize even small cardiac shunts.

Estimation of the Volumes of Blood in the Right Heart, Left Heart and Lungs in Intact Man by Radioisotope Techniques

William D. Love, Lawrence P. O'Meallie, and George E. Burch, New Orleans, La.

Development of an innocuous external isotope method for measuring intracardiac and pulmonary blood volumes would improve clinical diagnosis and advance the study of abnormal cardiopulmonary physiology. Such a technic has been studied in 38 patients.

The cardiac surface projection was outlined fluoroscopically and precordial lead shielding was arranged so that a 2×2 inch scintillation crystal 25 cm. from the anterior chest recorded only radioactivity from the cardiac area. Accumulated counts were recorded, each one-third or one-half second after intravenous injection of 100 μc . radioiodinated human serum albumin. Intracardiac blood volume was calculated from precordial radioactivity 10 minutes after injection and the simultaneous whole blood radioactivity. Geometrical and absorption corrections were determined in phantoms. In 16 normal subjects, intracardiac blood volume was 345 ± 55 ml. per M^2 body

surface. In subjects with heart disease, volume was 295 to 1,180 ml. per M^2 .

Right- and left-sided components could be separated in 23 by extrapolating exponential rates of decline of precordial radioactivity. Volumes were proportionate to the areas of the separate curves, assuming comparable geometry. Normal right- heart volume was 170 ± 25 ml. per M^2 and left-sided, 185 ± 50 ml. per M^2 . With heart disease, these were 130 to 365 ml. per M^2 and 150 to 460 ml. per M^2 , respectively. In these 23 subjects, pulmonary blood volume was calculated from cardiac output and mean circulation time from right-to-left heart. One-half of the intracardiac volume was subtracted. Values in normals were 490 ± 130 ml. per M^2 and with heart disease 520 ± 150 ml. per M^2 .

Effect of Liver Damage on Renal-Hypertensive Rats

Hubert F. Loyke, John J. Plucinsky, and Thomas L. Crawford, Cleveland, Ohio

The clinical observation has been made by many that liver disease and hypertension do not coexist. It therefore seemed wise to see if the laboratory animal would parallel man.

A total of 32 albino rats were used for the study. Six rats served as controls and the remaining 26 were made renal hypertensive by the Grollman procedure. Blood pressures were recorded with the Freedman microphone from the rats' tails. The average systolic pressure was 220 mm. in the renal hypertensive group and 150 mm. for the control animals. Carbon tetrachloride injections were then given biweekly to 21 of the hypertensive rats. All of these animals had blood pressure reductions of 40 mm. or more, the average being 74 mm. The control animals' pressure averaged 150 mm. Varying degrees of liver damage and albumin/globulin ratio changes were associated with the blood pressure reduction. Upon cessation of the carbon tetrachloride injections, the blood pressures returned to their previous hypertensive levels in all of the animals. Morphologic studies revealed that only a moderate degree of fatty metamorphosis is necessary to cause the blood pressure to fall from hypertensive levels to normotension.

Cause of Dyspnea in Chronic Congestive Heart Failure

Peter C. Luchsinger,* Thomas J. Ryan, and Kenneth M. Moser, Washington, D.C.

Prior attempts to define the functional basis of cardiac dyspnea have emphasized either the hemodynamic or the ventilatory abnormalities in-

volved. In the present study, right heart catheterization was combined with detailed pulmonary function testing in an effort to provide a broad, integrated explanation of cardiac dyspnea.

In 14 patients with congestive heart failure of various etiology, the respiratory mechanics were determined during or immediately following right heart catheterization. In all patients the pulmonary artery and pulmonary wedge pressures were either elevated or at the upper limits of normal. The cardiac output was uniformly diminished. Minute ventilation was increased. Detailed analysis showed that this hyperventilation was primarily a manifestation of increased dead space ventilation while alveolar ventilation remained normal or was slightly increased. Respiratory rate was accelerated and the tidal volume was low. Effective compliance was decreased in all patients, averaging .115 L. per mm. H₂O. Relatively normal values were found in terms of respiratory work per liter of ventilation. However, the respiratory work per minute was definitely elevated (.26-.64 Kg./m/M) due to the increase in minute ventilation.

Conclusions: Patients with pulmonary congestion have an increased work of breathing per unit time. This is chiefly due to an increase in minute ventilation but also reflects the slight increase in nonelastic resistances. The increase in minute ventilation is explained by the elevated respiratory rate, which, in turn, appears related to the decreased compliance. In this group of patients, there was no consistent correlation between respiratory mechanical and pulmonary hemodynamic abnormalities.

Pulmonary Stenosis with Defective Development of the Right Ventricle (and Intact Ventricular Septum)

Mary J. Luke, Catherine A. Neill, and Helen B. Taussig, Baltimore, Md.

During the past 11 years, we have had 11 patients (2 males, 9 females; age range 5 weeks to 4 years) with extreme valvular pulmonary stenosis and small valvular ring, markedly thick-walled right ventricle with small chamber and abnormal tricuspid valve. There was cyanosis at, or shortly after, birth, slow development and poor weight gain. Most cases had cardiomegaly similar to that in PPS but without poststenotic dilatation, a large right atrium even before the onset of failure, and hepatomegaly with pulsation. In 3, such cardiomegaly was absent and the clinical picture resembled tetralogy of Fallot. A harsh systolic murmur with systolic thrill and diminished P₂, suggestive of PPS, were noted in most cases.

Electrocardiogram was significant: axis predominantly right, tall peaked P waves, RV₁ 5 mm., or less, in the majority and never over 20 mm. Lack of great right ventricular hypertrophy differed from typical PPS and absence of left ventricular hypertrophy from tricuspid atresia. Angiocardiography showed a large right atrium with shunting to the left atrium, small right ventricle and tight valvular pulmonary stenosis. A right heart catheterization, atrial pressure was elevated and ventricular pressure usually was below 100 mm.

Differential diagnosis in infants included PPS, rarely Ebstein's malformation or tricuspid atresia over 2 years, without cardiac failure, tetralogy of Fallot. Accurate diagnosis is important because early death or rapidly progressive cardiac failure followed anastomosis in 5 cases. Transventricular valvotomy seems inadvisable because of the thick wall and very small chamber. Valvotomy under hypothermia and direct vision gave remarkable improvement in 2 cases.

Obstructive Ventricular Hypertrophy in Congenital Heart Disease: Definition, Classification, and Surgical Importance

Paul R. Lurie, Harris B. Shumacker, Jr., Dale M. Schulz, Eugene C. Klatte, Indianapolis, Ind., and Maria Z. Grajo, Manila, Philippines.

Obstructive ventricular hypertrophy is defined as that condition wherein a ventricle with a thick, strong wall produces obstruction to blood flow. The three subtypes are: outflow, septal, and generalized. (1) The obstruction may be produced by hypertrophy at the outflow portion of the ventricle alone, essentially confined to late systole; (2) the whole septum may be extremely thick and encroach in systole upon 1 or both ventricles and reduced diastolic volume as well; or (3) the whole ventricle may be generally involved, the resistance to stretching of the thick wall causing reduced diastolic volume. The condition develops either in the embryonic or early childhood periods, usually in response to the stress of outflow obstruction. The outflow sub-type has been reported also, with the stress of excessive volume work.

This paper does not claim to report a unique or original observation. Rather, it unifies previously unrelated phenomena, proposes a classification and calls attention to the bearing of obstructive ventricular hypertrophy upon complete cardiac repair as essayed with open-heart techniques. The material is a group of abbreviated case reports, including cineangiograms, photographed autopsy material, and diagrams. In some instances,

complete surgical alleviation of named discrete lesions failed because of neglect to consider the obstructive ventricular hypertrophy. In other instances, because of recognition of obstructive ventricular hypertrophy, unorthodox surgical procedures were planned and resulted in highly favorable outcomes. While quantitation of this type of lesion is desired, until methods of measurement are developed, its qualitative recognition by cardiography will be important.

Physiologic Studies of the Natural Course of 33 Infants and Children with Ventricular Septal Defects

Joshua Lynfield, Benjamin M. Gasul, and Lawrence L. Luan, Chicago, Ill.

Of more than 400 patients with ventricular septal defects studied clinically during the last 12 years, 130 had cardiac catheterizations, and of these, 33 had 2 or more cardiac catheterizations. Fourteen were under 1 year at the first catheterization. Seven were between 1 and 2 years, and 10 between 2 and 6 years. The interval between the first and second catheterization in 26 patients was 2-5 years, and 1-7 years in the remainder.

The pulmonary artery systolic pressure was over 60 mm. Hg in 18 patients. In 13 patients, 11 of whom were under 2 years of age, the pulmonary artery systolic pressure fell by an average of 20 mm. Hg and the pulmonary flow index decreased in 8.

The pulmonary pressure remained substantially unchanged in 14 patients, 9 of whom had a pressure above 60 mm. Hg. In 3 patients the pulmonary pressure and resistance index increased. Only 1 of the 33 patients developed a bidirectional shunt.

Three patients subsequently developed hemodynamic evidence of a considerable pressure gradient at the right ventricular outflow tract. Those with pressure below 40 mm. Hg showed no rise with age. Not a single medical death occurred in this group of 33 patients. In the group of 130 patients who had cardiac catheterization, only 1 mentally retarded patient aged 18 months died of associated bronchopneumonia. Our findings demonstrate that infants with large ventricular septal defects do not have a tendency to develop rapidly progressive pulmonary hypertension. Furthermore, infants with pulmonary hypertension frequently show regression of the pulmonary pressure toward normal.

Hemodynamic Findings in 30 Patients Below One Year of Age with Ventricular Septal Defects

Joshua Lynfield, Benjamin M. Gasul, and Lawrence L. Luan, Chicago, Ill.

Clinical and cardiac catheterization studies were performed on 30 infants age 3 to 12 months with ventricular septal defects. The pulmonary artery systolic pressure was under 40 mm. Hg in 9, between 40 and 60 in 13, and over 60 in 8. The pulmonary flow index averaged 10.2 L. in those whose pulmonary pressure was below 40 mm. Hg, 11 L. in those between 40 and 60, and 8.7 L. in those above 60.

The total pulmonary resistance index was normal in those with a pulmonary pressure below 40 and in all except 3 with a pressure between 40 and 60. In 6 of 8 patients with a pressure above 60, it averaged 720 dynes sec. cm.⁻⁵ In 1 it was normal and in another it could not be calculated.

A bidirectional shunt predominantly from left to right was present in only 1 patient.

Heart failure developed in 9 infants with pulmonary hypertension. All recovered on medical treatment. In 5 of these infants heart failure appeared to be due to a considerably increased pulmonary blood flow associated with a normal pulmonary resistance index. In 3 infants it appeared to be related to a markedly elevated pulmonary resistance index. Flows could not be calculated in 1 infant.

Nineteen patients have been followed for 2 or more years, and 11 for 1-2 years.

Our findings demonstrate a high incidence (70 per cent) of pulmonary hypertension in infants with ventricular septal defects. All infants in heart failure recovered with proper medical treatment. No medical death occurred in the whole group. The relationship of pulmonary pressure, pulmonary flow index, and pulmonary resistance index to heart failure in infancy has been studied.

Relative Effect of Chronic Ischemia and Myocardial Revascularization Procedures on the Ventricular Fibrillation Threshold

Lloyd D. MacLean, Clifford M. Phibbs, and Louis M. Levy, St. Paul, Minn.

The relative effectiveness of chronic ischemia and of 2 myocardial revascularization procedures in elevating the ventricular fibrillation threshold following acute coronary artery occlusion has been studied in 84 dogs. The electronic equipment used permitted precise quantitative measurements of threshold changes. An initial fibrillation threshold was determined in all animals without and with temporary occlusion of the anterior descending coronary artery. The animals were divided into four groups: Group 1, 31 dogs were controls; group 2, 20 dogs were subjected to cardiac poudrage; group 3, 25 dogs

underwent internal mammary artery implantation. Chronic, mild ischemia was produced in one-half of the animals in each of the first 3 groups by ligating branches of the circumflex and anterior descending coronary arteries. Group 4, 8 dogs, underwent permanent ligation of the main left anterior descending coronary artery. The initial determination of threshold with temporary coronary occlusion produced a marked drop in fibrillation threshold in all dogs. This was not altered significantly by chronic mild ischemia or cardiac poudrage when these animals were retested 6 months later. Massive ischemia resulted in a moderate elevation of threshold after 6 months. A striking and highly significant elevation of fibrillation threshold was observed in the animals with internal mammary artery implantation when retested with coronary occlusion after 6 months. These studies suggest that considerable protection from ventricular fibrillation due to myocardial ischemia is offered by surgical means, while chronic ischemia is much less effective in achieving this protection.

Rarity of Hypertensive Disease in Paraplegics

Joseph H. Magee, Allan M. Unger, and David W. Richardson, Richmond, Va.

The incidence of sustained hypertension in a group of 1,100 paraplegics with neurogenic bladders has been approximately 3 per cent. Clearance studies have shown progressive decreases in renal function, presumably due to pyelonephritis, and enhanced by vesicoureteral reflux. Seventeen patients, in whom the latter complication has consistently involved only a single ureter, have been studied by clearance technics after ureteral catheterization.

All were normotensive and without pyelographic abnormalities. Seven had no functional disparity (right minus left/mean < 15 per cent, as proposed by Baldwin et al.). Three had disparity in C_{In} and C_{PAH} , but not in V or C_{Osm} . The remaining 7 also had reduced V and C_{Osm} in the kidney with reduced C_{In} and C_{PAH} . Some (but not all) patients, both with or without disparity, had denervation of the visceral vascular bed, as judged by sweat patterns.

Four other patients, without cord injury, had in kidneys subsequently removed for relief of hypertension, a like pattern of reduced V and C_{Osm} , associated with reduced C_{In} and C_{PAH} . Pathologic examination revealed sclerotic main renal artery lesions in 2 and chronic pyelonephritis in 2.

Identical patterns of functional disparity thus were found with, and without, associated hyper-

tension. Fundamentally similar lesions may be responsible, spinal cord injury altering vascular reactivity and conferring protection against otherwise inherent hypertensive diathesis. An alternate hypothesis is that this renal functional pattern identifies predominantly unilateral pyelonephritis with diverse predisposing factors. The pyelonephritis found in surgically remediable hypertension may be secondary to an initial ischemic producing vascular process.

Determination of Cardiac Output with Radioactive Iodinated Human Serum Albumin: Clinical Value

Donald V. Mahony, Fullerton, Calif., Balakrishna Hegde, and Franz K. Bauer, Los Angeles, Calif.

Determination of cardiac output with radioactive iodinated human serum albumin is helpful in the evaluation of suspected cardiovascular disease when the usual diagnostic tests are equivocal or negative, according to findings in over 100 determinations using this technic. Measurement of cardiac output before and after a standardized exercise test permits assessment of cardiac reserve; although the normal individual usually can increase his cardiac output approximately 100 per cent with exercise, patients with limited cardiac reserve due to rheumatic or atherosclerotic heart disease, thyroid disease, or other acquired or congenital conditions may be able to increase cardiac output only slightly with exercise. We have found the procedure especially helpful in determining the diminution, if any, in cardiac reserve after myocardial infarction, in differentiating high or low output failure from normal output, in the study of intracardiac shunts, and in evaluating the results of cardiac surgery. As this procedure employs simple venipuncture rather than the more traumatic arterial puncture, determination of cardiac output with radioactive iodinated serum albumin can be used even during the acute stage of myocardial infarction, with subsequent measurements at 1 or 2 weeks after the attack to assess diminution of cardiac reserve and permitting individualization of treatment.

Hyperlipemia and Intravascular Clotting

Emanuel E. Mandel, Hossein D. Fahimi, and Jack Lazerson, Chicago, Ill.

An attempt was made to determine whether the previously observed in vitro phenomenon of "lipogenic hypercoagulability" reflected increased tendency to clot formation in vivo. The femoral and jugular veins of anesthetized dogs were surgically freed and isolated by means of serafin

clamps. At selected intervals, small vein segments were excised, and their contents carefully examined for presence of a fibrin clot. The interval from the moment of clamping the veins (of 1 cm) until excision of the vein segment containing the first visible clot was designated as intravascular clotting time (ICT).

There was remarkable consistency in ICT values between the left and right side of fasting dogs (normal range: 30-40 minutes). When a 15 per cent cottonseed oil emulsion, containing 1.2 per cent soybean phosphatide, was injected intravenously, distinct shortening of ICT (5-20 minutes) usually occurred, coinciding with maximal serum turbidity and triglycerides.

The same degree of lipemia-induced shortening of ICT was observed in dogs, either pretreated with bishydroxycoumarin or receiving a constant infusion of heparin in saline. While a tendency to prolongation of ICT was apparent in the fasting state, injection of the emulsion was regularly followed by ICT shortening, both in markedly hypoprothrombinemic animals (prothrombin < 10 per cent) and in mildly heparinized dogs (thrombin time doubled or tripled). While the thrombogenic effect of this intravenously-induced lipemia (phosphatides?) remains to be elucidated, these studies provide new evidence that anticoagulation is not synonymous with antithrombotic effect.

Use of an Organic CO₂ Buffer (THAM) in the Treatment of Patients with Severe Respiratory Failure and CO₂ Narcosis

Felice Manfredi, Angelo P. Spoto, Herbert O. Sieker, and Herbert A. Saltzman, Durham, N.C.*

Patients with chronic lung disease and acute respiratory failure may develop CO₂ narcosis with associated circulatory and neurologic disorders. Mechanical respirators, antibiotics, cardiotonic therapy, and other measures are not always life-saving.

Recently, organic CO₂ buffers have been reported useful for experimental CO₂ narcosis in animals. It was suggested this type of compound might be employed in patients with CO₂ retention.

For this reason the organic CO₂ buffer (trihydroxymethylaminomethane, THAM) was given on 4 occasions to comatose mechanically ventilated chronic lung disease patients in acute CO₂ narcosis with arterial pH values of 6.95-7.30, and CO₂ limits of 90-133 mm. Hg. THAM was fused as a 0.33M I.V. solution in 0.2 per cent line, at a 300 ml. per hour rate, for 1-3 hour periods. Serial arterial blood and urine specimens

were analyzed for CO₂ tension, O₂ saturation, and electrolyte concentrations.

Infusions of THAM produced consistent marked changes in arterial CO₂ tension and pH. Maximal changes from pretreatment values for arterial blood were a rise in pH from 7.243 to 7.34, and a comparable fall in pCO₂ from 106 to 92 mm. Hg. The serum total CO₂ content showed a small mean increase from 102.07 to 106.85 volumes per cent. Arterial O₂ saturation, serum electrolytes, and urinary volumes or electrolytes did not change significantly. Clinically, the patients appeared to respond more readily to conventional therapy even though favorable blood gas changes proved transient.

Organic CO₂ buffers can be used safely in human subjects to increase the blood pH and decrease the pCO₂ in acute respiratory acidosis and acute CO₂ intoxication due to cardiorespiratory failure.

Studies of Peripheral Circulation During Sickle Cell Crisis

Felice Manfredi, Angelo P. Spoto, Herbert A. Saltzman, and Herbert O. Sieker, Durham, N.C.*

Sickle cell disease (SCD) patients commonly demonstrate arterial oxygen unsaturation. In addition, venous oxygen saturations of arterial magnitude were reported in this group recently. This phenomenon was studied in 25 SCD patients, including 6 subjects in hemolytic crisis, plus 9 febrile anemic patients without SCD.

Cournand needles were placed in a brachial artery, superficial vein, and deep vein of one upper extremity. Paired arterial and venous blood samples were analyzed for O₂ content, O₂ saturation, hemoglobin, hematocrit, and pH.

Six SCD patients studied during crisis averaged a 2 per cent oxygen saturation decrease and 0.015 pH units fall between arterial and superficial venous paired samples. Arterial-deep venous differences in oxygen saturation and pH were greater than 20 per cent and 0.03 units in all cases. Arterial means were 86 per cent for oxygen saturation and 7.388 for pH.

Twenty-five SCD patients not in crisis, including 6 subjects restudied after acute episodes had subsided, displayed means of 19.8 per cent oxygen saturation decrease and 0.036 pH units fall between arterial and superficial venous pairs. Arterial means were 87.4 per cent for oxygen saturation and 7.374 for pH. Nine febrile or anemic patients without SCD demonstrated mean values of 20.1 per cent oxygen saturation decrease and 0.032 pH units fall between arterial and superficial venous paired samples.

The results indicate that arterialization of superficial venous blood is a phenomenon associated with sickle cell crisis. A-V shunting appears the most rational explanation. Clinically, the presence of arterialized blood in superficial veins may be a laboratory help in establishing the existence of crisis in cases where other findings are not conclusive.

Appraisal of Indicator-Dilution Technic in the Measurement of Myocardial Blood Flow

Thomas L. Marchioro, J. Cuthbert Owens, James Lister, Vernon Montgomery,* and Henry Swan, Denver, Colo.

An attempt to measure myocardial blood flow in the intact animal is described.

Using RIHSA, the cardiac output was measured by the indicator-dilution technic. A similar formula which had been proved valid on a model circulation was applied to measuring the regional blood flow through the coronary circuit. A Cournand catheter was placed in the distal pulmonary artery through the jugular vein; this was used for injection of RIHSA. A polyethylene catheter in the pulmonary artery with its tip proximal to that of the Cournand catheter was used for withdrawal of blood for continuous monitoring for radioactivity.

If the coronary circuit was shorter than other circuits, the first activity found in the blood withdrawn from the pulmonary artery would be coming from the coronary circuit and the coronary flow could thus be measured.

Data show that the method is impracticable in the dog because there is an insufficient time interval between the appearance of coronary blood and that from other circuits in the pulmonary artery. Simultaneous monitoring of pulmonary artery and superior vena cava in 3 animals showed that the circulation time through the coronary circuit and the most rapid noncoronary circuit was, for practical purposes, equal.

Estrogen Administration in Postmyocardial Infarction: Increased Long-Term Survival and Other Beneficial Effects

Jessie Marmorston, Oscar Magidson, Beverly Hills, Calif., Oliver T. Kuzma, Frederick J. Moore, Los Angeles, Calif., and Jack J. Lewis, Beverly Hills, Calif.

Efficacy of small and moderate dosages of estrogen in lowering abnormally elevated serum lipids and increasing long-term postinfarction survival in men and in postmenopausal women has been studied in special clinics. Three groups of patients have been studied: (1) 51 pairs of

women, closely matched as to age, date of myocardial infarction, and complication; (2) a group of 168 women patients with myocardial infarction, randomly assigned to treatment and control groups; and (3) 109 men patients with myocardial infarction, randomly allocated to subgroups, treated with small to moderate dosages of estrogen or placebo.

In the 3 groups, estrogen has proved efficacious both in altering serum lipid patterns toward normal and in increasing long-term postinfarction survival. One of the most striking findings is the protective effect of estrogen support in diabetic patients with myocardial infarction wherein estrogen overcomes the notable tendency of these patients to develop additional cardiovascular complications.

Cardiospectrographic Analysis in Acquired and Congenital Heart Disease

Daniel Mason and Norman B. Burke, Philadelphia, Pa.

With a specially constructed tape recorder and suitable dynamic microphone, accurate simultaneous representation of all frequency-intensity responses of heart sounds and murmurs were recorded from the precordium in patients with acquired valvular and congenital defects.

These tape recordings were subjected to spectrographic analysis in which all of the frequency and intensity components in any given instant in a cardiac cycle were portrayed (cardiospectrograms).

Correlation with other physiologic data (pressure gradients, velocity of blood flow, etc.) was carried out. It was noted that the frequency-intensity response of a murmur varied directly with the pressure gradient and rate of blood flow across a valvular or ventricular septal defect.

The effects of respiratory effort also were studied. Definite augmentation of frequencies and intensity was noted, for example, in tricuspid stenosis and tricuspid insufficiency during the inspiratory phase.

Three heart sound combinations such as close and wide splitting of S₂, opening snap, and diastolic gallop rhythm also were analyzed, and typical cardiospectrographic patterns were noted.

It was recognized further that the human ear could not accurately define these auscultatory findings because of inherent inability to interpret correctly the responses in terms of pitch and loudness as compared with the recorded frequencies and intensities. Often increased pitch (dependent on certain frequencies in an auscultatory event) was misinterpreted by the listener as "loudness."

Cardiospectrographic analysis also accurately delineated intensity in each of the frequency zones present, thus apparently allowing for more definite representation than that seen in the usual oscilloscopic phonocardiogram.

Therapy and Other Factors Influencing the Course of Rheumatic Heart Disease

Benedict F. Massell, Shekhar Jhaveri, and Gabor Czomiczer, Boston, Mass.

Significant murmurs indicative of rheumatic valvular disease sometimes disappear with subsidence of acute rheumatic fever and during subsequent follow-up, but the factors influencing such disappearance have not been clearly defined. This problem has been studied in 484 patients, observed in an initial attack and followed for periods up to 9 years since hospital discharge. A 50.6 per cent incidence of valvular involvement on admission decreased to 41.1 per cent at discharge, 38.6 per cent at 1 year, 34.5 per cent at 2 years, 32.0 per cent at 5 years, and 26.8 per cent at 9 years.

Incidence of complete disappearance of significant murmurs during hospitalization in 245 patients with valvular involvement was related to interval between onset of attack and admission to hospital. Thus, disappearance occurred in 26.4 per cent of 91 patients, ill 1 to 14 days; in 18.4 per cent of 76, ill 15 to 42 days; and in 11.5 per cent of 78, ill longer than 42 days. The influence of therapy is suggested by the complete disappearance of significant murmurs during hospitalization in 33.8 per cent of 80 patients with carditis, treated with large amounts of adrenocortical steroids for 12 weeks, and in only 12.1 per cent of 165 patients with carditis, not so treated. This difference is not influenced by the factor of duration of illness, prior to beginning of therapy. Other factors which influence the course of rheumatic heart disease during hospitalization and follow-up are: heart size, presence of congestive failure or pericarditis, intensity of systolic murmurs, and presence of mitral or aortic diastolic murmurs.

Premonitory Phase of Coronary Occlusion: Results in Patients Receiving No Anticoagulant Therapy

Arthur M. Master, New York, N.Y.

Observations were limited to a study of 80 consecutive patients who abruptly developed increased frequency and severity of chest pain, accompanied by many new qualities. Although there was time to administer anticoagulants, this was not done in this control series.

Patients who sustained 1 or more isolated episodes of severe chest pain were not included, since infarction may have already taken place. The impending phase ranged from a few days to 2 months. In the majority, the white blood count, sedimentation rate, and transaminase reaction study were either normal or slightly increased. Where the white count rose above 10,000, the sedimentation rate above 30 mm. or the transaminase reading above 50 units, the patients had developed coronary insufficiency or coronary occlusion. The major electrocardiographic changes were RS-T depressions and/or T wave inversions, which appeared in 55 instances. If tracings were taken frequently enough in every instance, practically all patients would show electrocardiographic alterations. At the conclusion of the study no acute coronary episode had occurred in 61 of the 80 patients; 14 had developed coronary insufficiency, 3 had suffered coronary occlusion (2 of whom died) and 2 developed status anginosus.

Our results appear to be better than any previously published series, whether or not anticoagulants were employed. However, to judge the efficacy of anticoagulant medication, a series of patients are now being studied who are being given this therapy.

Master Two-Step Exercise Electrocardiogram: Exclusion of the "False-Positive"

Arthur M. Master, Ephraim Donoso, and Isidore Rosenfeld, New York, N.Y.

The purpose of the Master 2-step exercise electrocardiogram is to establish the diagnosis of coronary artery disease objectively, by means of electrocardiographic changes after standard exercise, and to differentiate between cardiac and noncardiac chest pain.

A normal resting electrocardiogram does not exclude coronary artery disease. We have found 45 per cent of patients with angina to have negative resting tracings, and 1 report says the incidence is as high as 70 per cent. This is so because, at rest, the coronary circulation may be adequate, but under mental or physical stress, it is not.

After exercise, an RS-T depression of more than one-half millimeter in any lead must be evaluated. In this regard, the type of RS-T depression has proven of great value. The "J" (junctional) type is probably of much less importance than so-called "ischemic changes," viz., horizontal or sag depressions. Minor T wave changes and transient arrhythmias are of no or very little significance. Chest pain alone, without concomitant electrocardiographic changes, does not constitute a positive test.

Using these criteria, in normal subjects, the 2-step test is usually negative. A "false-positive" result is occasionally seen in apparently normal people, particularly those who are nervous. However, analysis of the shape of the RS-T segment depression excludes the vast majority of such "false" positives. If the 2-step test is performed under basal conditions, even fewer false positives will appear. This reduction of false positives has greatly enhanced the value of the test.

"Standardization" of the Master Two-Step Exercise Electrocardiogram

Arthur M. Master, Ephraim Donoso, and Isidore Rosenfeld, New York, N.Y.

Unstandardized modifications of the Master 2-step test are frequently employed. The results are unreliable. The 2-step test must be standardized according to age, sex and weight. Thus, in patients with angina pectoris, the single (1½ minute) test may be negative, but the double (3 minute) test will be positive. In a second group, if the time is kept constant but the number of trips decreased below that in the published tables, a positive test will become negative. This can be repeated time and again. In other words, too little exertion even in a patient with severe coronary disease may result in a negative test. In a third group of patients the number of trips was increased, rather than decreased, but the time was maintained constant at either 1½ or 3 minutes. In these cases a previously negative result after exercise could become positive. Again standardization is necessary, for if 1 investigator demands more work of the same patient than does another, different results may be obtained. In a general way, the electrocardiographic changes in the positive tests are quantitative. The greater the work performed, that is, the more trips by the same patient in the same interval of time, the more pronounced and persistent will be the changes. To follow the course of the patient's angina pectoris a definite technic must be pursued. Finally, in a normal person excessive exercise may produce alterations in the electrocardiogram.

The "standardization" of the test has made it possible to perform physiologic and pharmacologic research.

Hypotensive Properties of a New Monoamine Oxidase Inhibitor: DL-Serine-N²-Isopropylhydrazide

Morton H. Maxwell, Samuel I. Roth, Morton L. Pearce, and Charles R. Kleeman, Los Angeles, Calif.

The hypotensive properties of a new monoamine oxidase inhibitor, chemically related to iproniazid but containing serine, dl-serine-N²-isopro-

pylhydrazide (RO4-1038), were investigated. Patients were selected from a "study" group of individuals with relatively stable essential hypertension of mild to moderate severity. Following a control period of placebo therapy, oral administration of RO 4-1038 twice daily resulted in a progressive decrease of blood pressure, generally most marked in the upright position and reaching a plateau in 2 to 3 weeks. The hypotensive effect was considerably enhanced by the simultaneous administration of chlorothiazide (dose: 250 to 500 mg. twice daily). With patients serving as their own controls, the hypotensive action of RO 4-1038 (average dose: 20 mg. daily) was greater than that of combined reserpine and chlorothiazide therapy. The simultaneous use of RO 4-1038 (average dose: 10 mg. daily) and chlorothiazide had a hypotensive effect equivalent to that of ganglionic blocking agents in the usual therapeutic dosage. No drug tolerance developed during continuous administration of RO 4-1038 for as long as 4 months. There was no evidence of renal, hepatic, central nervous system or hematologic toxicity.

In 16 patients, the following average blood pressure reductions were achieved. Group A: Supine, placebo 193/105, RO 4-1038 162/93; standing, placebo 194/116, RO 4-1038 131/87. Group B: Supine, placebo 204/122, RO 4-1038 plus chlorothiazide 141/90; standing, placebo 212/131, RO 4-1038 plus chlorothiazide 110/80.

It is concluded that the new monoamine oxidase inhibitor, RO 4-1038, is a very potent hypotensive agent. Since monoamine oxidase inhibitors increase circulating norepinephrine and serotonin, it is suggested that, in man, the usual vasoactive adjustments to the erect position may be mediated by metabolic products of naturally occurring pressor amines, rather than by the amines themselves.

Control of Anticoagulant Therapy by the Standard Clotting Time in 1,000 Consecutive Cases

George A. Mayer and W. Ford Connell, Kingston, Canada

The standard clotting time (Mayer) measures the over-all coagulability of the blood by a highly reproducible technic. It utilizes unmodified venous blood in uncoated capillary glass tubes. During the past 5 years, it has been used at the Kingston General Hospital as the sole therapeutic control in 1,000 consecutive hospitalized patients. We can now report: 1. Six oral anticoagulants produced significant prolongation of the S.C.T. in all patients receiving adequate dosage. 2. Despite marked chemical differences, all anticoagulants required an induction period of 3 to 5 days. There are marked individual differences in responses to identical

oses of the same drug. 3. Neither age, sex nor weight proved reliable determinants of induction dosage. 4. For the first 3 to 5 days, intravenous heparin, 100 mg. every 6 to 10 hours, is essential, further thrombosis is to be avoided. 5. Dissipation of anticoagulant effect requires 3 to 8 days with bishydroxycoumarin, 24-48 hours with acenocoumarin, phenindione and anisindione. Marked individual variations were noted, however. 6. With the S.C.T. in the therapeutic range, neither thrombo-embolism nor hemorrhage have occurred. 7. When the S.C.T. is excessively prolonged by the oral anticoagulants, vitamin K₁ oxide, 20 mg. orally or intravenously, will reduce the test to a safe normal range within 5 to 8 hours. 8. The S.C.T. as the sole therapeutic control of anticoagulant therapy would appear to be definitely superior to the Quick one-stage prothrombin time.

Myocardial Necrosis Following Elective Cardiac Arrest Induced with Potassium Citrate

James A. McFarland, Lewis B. Thomas, Joseph W. Gilbert, and Andrew G. Morrow, Bethesda, Md.

Elective cardiac arrest, induced in the course of cardiac operations with cardiopulmonary bypass, has been found to be a valuable technical adjunct. Of the various methods available for producing elective asystole, the technic of Melrose, in which a solution of potassium citrate is infused into the coronary bed, has been most widely employed. Evidences of serious and sometimes fatal myocardial failure were observed following elective cardiac arrest by this method and prompted a pathologic study of its effects on the heart.

Systematic gross and microscopic examinations were made of the hearts of 30 patients who died following intraoperative operations with cardiopulmonary bypass. Nineteen patients had been subjected to elective cardiac arrest with 25 per cent potassium citrate in whole blood. In 15 of these 19 hearts a distinctive type of necrosis was observed in sections of the myocardium. The lesions were characteristically multiple and sharply circumscribed, and individual muscle fibers were hyalinized, granular and in various stages of disintegration. In the 11 patients in whom elective arrest with potassium citrate was not employed, no lesions of this type were observed.

The etiology of the necrotic lesion and its significance in the choice of a surgical technic have been investigated.

Circulatory Changes in Polyostotic Fibrous Dysplasia (Albright's Syndrome) Due to Arteriovenous Shunting

Henry D. McIntosh, William L. Gleason,* James M. Bacos, D. Edmond Miller, Durham, N.C., William R. Lewis, Bethesda, Md., and Sidney Grossberg, Baltimore, Md.

Increased arteriovenous shunting in areas of skeletal involvement has been demonstrated in osteitis deformans (Paget's disease). This study suggests that similar shunting accompanies polyostotic fibrous dysplasia (PFD).

Six female patients with typical roentgenographic evidence of PFD (biopsy confirmed in 5 cases) were studied. Three gave a history of precocious puberty and 5 had classical pigmentation changes. Cardiac indices (CI) were measured by the Fick method and regional arteriovenous oxygen differences (A-V O₂) were determined by multiple venous sampling.

The 3 highest CI's (5.6, 6.6, 4.6 L. per minute per M.²) were exhibited by the 3 youngest patients (ages 6, 31, 20, respectively). The 2 highest indices were found in the only 2 patients with alkaline phosphatase elevation (59, and 9 BU). Both had iliac A-V O₂ of less than 1.7 vol. per cent. The older of the 2 had extensive cranial involvement, an associated cranial bruit, a jugular A-V O₂ of 2.3 vols. per cent, and cardiomegaly.

The 3 older patients (ages 43, 48, 67) had normal or borderline CI's (2.9, 3.9, 4.1) and normal alkaline phosphatases. The striking feature in this group was a relative narrowing of the A-V O₂ across areas of skeletal involvement, as compared with similar areas free of disease.

This study indicates that, as in osteitis deformans, the skeletal involvement of PFD may be associated with considerable arteriovenous shunting. Such shunting may result in a high CI, cardiomegaly and local bruits. These data also suggest that the magnitude of the circulatory alterations may be related to the degree of activity of the osseous process, as estimated by the elevation of alkaline phosphatase, and that this activity diminishes with age.

Surgical Treatment of Coronary Artery Disease: Evaluation of Two Methods in a Large Series of Patients

J. Douglas McNair, Monrovia, Calif., Alfred Goldman, and B. J. Allenstein, Los Angeles, Calif.

This report concerns the results obtained in 34 patients with severe coronary artery disease who received surgery at the City of Hope Medical Center. Twenty-two patients received a pericardial poudrage, 1 a poudrage and Vineberg operation, 1 a poudrage and later an internal mammary ligation, and the remainder internal mammary ligation only.

All patients received careful pre- and postoperative examinations including electrocardiograms, rectocardiograms, orthocardiograms, and the usual blood and urine studies. During surgery many of the patients were studied by direct epicardial electrocardiograms. Since surgery, the patients have been followed for periods varying from 9 months to over 4 years.

Eighteen of the patients claimed some relief from their angina, varying from a temporary decrease in nitroglycerine need to complete freedom from angina and ability to return to gainful employment. Nine patients have died; 1 died 3 days following the Vineberg operation; 1 died 2 months after bilateral internal ligation; and 7 since having a poudrage. Four of those who died were examined post mortem.

An analysis of the results of this study would indicate that these types of surgery are of benefit in the relief of anginal pain, but that they do not prevent the progression of the coronary artery disease, as evidenced by further cardiac enlargement and the development of congestive heart failure and coronary thrombosis with myocardial infarction. There are also data to show that the poudrage does not prevent ventricular fibrillation; 1 patient died 21 months postoperative with electrocardiographic proof of ventricular fibrillation and 4 died suddenly at home, possibly of ventricular fibrillation.

Acyanotic Transposition of the Great Vessels

Ali Mehrizi and Helen B. Taussig, Baltimore, Md.

Acyanotic transposition of the great vessels means that the patient has a complete transposition of the great vessels but no cyanosis. During the past 10 years, we have seen 3 such cases. In each instance, a heart murmur was detected at birth. One of these patients showed slight cyanosis during the neonatal period which lessened during the first year of life. The others showed no visible cyanosis. All 3 patients showed cardiac enlargement, a harsh systolic murmur along the left sternal border and an accentuated pulmonic second sound. Fluoroscopy demonstrated that the heart was enlarged, there was fullness of the pulmonary conus and increased pulmonary vascularity. The electrocardiogram in each showed a right axis deviation and evidence of right ventricular hypertrophy but also some left ventricular hypertrophy. Hence, the condition closely resembled that of a ventricular septal defect and was suggestive of the early Eisenmenger type of ventricular septal defect in which there is no cyanosis during childhood. At operation or at autopsy, all of these children showed a complete transposition of the great vessels, the aorta arising entirely from the right ventricle and the pulmonary artery from the left, but there was a marked deviation of the ventricular septum and an even more extreme deviation than one sees in a Taussig-Bing malformation, so that the pulmonary artery and aorta come to lie side by side. There was, in addition, a large ventricular septal defect which was

mainly under the pulmonary artery. This malformation requires differentiation from a ventricular septal defect in which the great vessels are not transposed. The clue to the diagnosis was found in cardiac catheterization in which, in each instance, the saturation in the pulmonary artery was higher than that in the aorta.

Clinical Diagnosis of Renal Artery Constriction

Edward Meilman, New Hyde Park, N.Y., Abraham Azulay, Hicksville, N.Y., and John M. Butler, Cedarhurst, N.Y.

Five patients with renal artery constriction have been recognized by simple clinical criteria. The diagnosis was suspected because of: Acute onset of hypertension (duration of hypertension was 6 months to 8 years; age at onset varied from 27 to 58 years), negative family history, and specific finding of unilateral delay in dye excretion on intravenous pyelography.

The rapidity of first excretion of dye in the renal pelvis is a measure of renal blood flow in the absence of obstruction or intrinsic renal disease. Delay in the excretion on one side suggests diminished blood flow on that side. In 3 cases this delay was so brief that excretion appeared symmetrical on the usual 5 minute film; obvious unilateral delay was noted when the first film was taken at 3 minutes. For this reason, we now take IVP films in hypertensive patients at 3, 7, 10, 15 and 25 minutes. One patient with a double right kidney excreted dye first from the right lower kidney at 5 minutes, next from the left at 8 minutes, and finally from the right upper kidney at 15 minutes. Aortography showed constriction of 2 arteries (to the right upper and left kidney) and a normal vessel to the right lower kidney.

On the basis of the 3 criteria above, we made our first 5 referrals for aortography. All 5 patients showed renal artery constrictions proved by operation.

Further Observations Supporting the Enzyme Defect Theory of the Cause of Essential Hypertension

Milton Mendlowitz, Herbert L. Weinreb, Nosrat Naftchi, and Stanley E. Gitlow, New York, N.Y.*

Reactivity to 1-norepinephrine (NE) was determined in the digital circulation of 20 normotensive subjects and 20 patients with essential hypertension. The work of vasoconstriction per mg. of intravenously infused NE was measured both before and after the administration of prednisone or prednisolone. After 1 week of therapy, prednisone produced increase in NE reactivity in some but not all normotensive subjects but in none of

the hypertensive subjects, and after a single intravenous injection of prednisolone (100 mg.), NE reactivity was moderately increased in the normotensive but not in the hypertensive group. After 3 weeks of prednisone therapy (30 mg. daily), however, reactivity to NE was doubled or tripled in most subjects of the normotensive group, but remained substantially unchanged in the hypertensive group.

These observations support the theory that prednisone or prednisolone inhibits the enzyme which inactivates NE and that there is a deficit of this enzyme in essential hypertension. That the effect cannot be attributed to structural vascular changes is indicated by observations in 20 cases of Raynaud's disease both of the obstructive and vasospastic types where such structural changes as intimal hyperplasia and smooth muscle hypertrophy are known to occur in the digital arteries. NE reactivity was normal in both types of Raynaud's disease. Whether or not a hereditary deficit of the specific enzyme, O-methyl transferase, is the cause of essential hypertension can be established only by appropriate chemical studies.

Course of Total Pulmonary Resistance (TPR) Following Mitral Valvotomy

Joseph M. Merrill, Walter G. Gobbel, Jr., and Richard France, Nashville, Tenn.

The course of total pulmonary resistance (TPR) following mitral valvotomy has been investigated. To accomplish this objective the data from all patients who have had mitral valvotomy done in this hospital since 1952 and who have had preoperative determinations of TPR have been analyzed. An attempt has been made to restudy these patients at yearly intervals postoperatively. A total of 21 patients have now been studied. An average of 4 postoperative heart catheterizations per patient has been performed, the longest follow-ups being 7 years.

In this study, the lowest postoperative TPR value was considered to represent maximum benefit derived from surgery. In 11 patients, 29 months following operation, the TPR had fallen from an average preoperative value of 760 to an average postoperative value of 388 dynes sec. cm^{-5} . In 7 patients, 20 months after operation, the TPR had fallen from 903 to 661 dynes sec. cm^{-5} . In 3 patients, 28 months after operation, the TPR had risen from 554 to 668 dynes sec. cm^{-5} .

Of the 11 patients who derived maximum drop in TPR, 5 patients maintained their benefit for an average of 47 months. Two of these patients have developed greatly increased TPR 6 and 7 years following operation. Of the patients who gained little or no benefit from the surgical procedure, the value was calcified in all except 1. A

high preoperative TPR did not prevent a satisfactory postoperative fall, as the 3 patients with the highest preoperative values averaged a TPR of 2,055 dynes sec. cm^{-5} with a fall to 551 dynes sec. cm^{-5} following operation.

Production of Subendocardial Fibrosis in the Dog

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Though it is known that lymphatics drain the myocardium, they have been inadequately studied and their function is poorly understood.

Dogs were operated on through a left lateral chest approach and the major lymphatics draining the heart were visualized with the aid of Evan's blue dye injection into the myocardium. The lymphatic vessels were ligated and cut. The animals were re-operated on approximately 3 months after cardiac lymphatic ligation. Those dogs with demonstrable significant obstruction to lymphatic flow were shown at autopsy to have developed substantial subendocardial fibrosis.

Our studies indicate that chronic impairment of lymphatic flow from the myocardium causes significant anatomic alterations, the most striking being subendocardial fibrosis. These findings may be pertinent in explaining similar pathology in certain types of human diseases of unexplained etiology.

Effects of Various Catecholamines on Specific Hemodynamics when Given to Hypotensive and Normotensive Subjects

Lewis C. Mills and John H. Moyer, Philadelphia, Pa.

A large variety of catecholamines is available for the treatment of shock. Aside from differences in potency and duration of action, there also appear to be differences in their ability to react with adrenergic receptors in various vascular beds.

The effects of mephentermine, metaraminol, phenylephrine, norepinephrine, epinephrine, and methoxamine on renal hemodynamics were studied in normotensive and hypotensive dogs and humans. For a given rise in mean blood pressure in normotensive subjects, mephentermine had little effect on renal hemodynamics, whereas methoxamine produced a marked reduction. Other agents had an intermediate effect; in hypotensive dogs, infusion of mephentermine led to an increase in renal hemodynamics, whereas methoxamine did not. Again, the other agents had intermediate effects. In hypotensive humans, various results occurred depending on whether or not blood was replaced simultaneously, the etiology of the shock, and the agent used.

In a limited number of subjects, the effects of norepinephrine and metaraminol on cerebral hemodynamics were measured. In these subjects, hypotension was produced by ganglionic blockade. In general, cerebral blood flow was restored to normal when the blood pressure was elevated.

Hemodynamic Effects of Tetraethylammonium Chloride in Hypertensive States, with Observations on the Specificity of the "TEAC Test"

John H. Morledge and Lloyd R. Rudy, Seattle, Wash.

This study was undertaken to ascertain the diagnostic specificity of the "TEAC test" in clinical hypertension and to define the hemodynamic changes producing the blood pressure responses observed.

Twelve hypertensive subjects (8, essential hypertension; 2, coarctation; 1, pyelonephritis; 1, unilateral renal artery stenosis (RAS) studied pre- and postoperatively) were studied supine with cardiac catheterization and continuous brachial artery recording. Control observations were followed by 400 mg. TEAC intravenously; pressure changes were maximum during the fourth to sixth minutes following TEAC. Hemodynamic data were redetermined during this interval.

All 8 essential hypertensive patients displayed falls in arterial pressure with TEAC (depressor response). A marked fall in systemic resistance without change in cardiac index appeared in those with failure. In those without failure both cardiac index and systemic resistance fell moderately. Two coarctation subjects had depressor responses, accompanying a slight fall in flow and a moderate fall in resistance. The pyelonephritic hypertensive subject displayed no post-TEAC pressure change. Flow decreased moderately, however, with an equivalent increase in resistance. Preoperatively, the RAS subject showed a rise in diastolic pressure with TEAC (pressor response), due to a slight decrease in flow and a rise in resistance. Postoperatively, he acquired a TEAC depressor response with marked decrease in resistance and slight increase in flow. Except for the preoperative RAS subject TEAC uniformly induced a decrease in calculated left ventricular work. Stroke index decreased in all subjects.

The TEAC test appears to be a useful diagnostic tool in some forms of hypertension. The different underlying hemodynamic responses suggest distinct pathogenic mechanisms in the several forms of hypertension studied.

Fourth Heart Sound: Studies with Intracardiac Phonocardiography

Howard L. Moscovitz, Ephraim Donoso, Ira J. Gelb, and Edward Henry, New York, N.Y.

Differences of opinion exist concerning the mode of production of the atrial sound, the nature of its components, and the extent of its participation in the first heart sound complex. An intracardiac microphone facilitates study of the fourth heart sound, since it can detect sound vibrations at their site of origin without attenuation by transmission through lung and chest wall structures.

Intracardiac microphones, utilizing barium titanate pick-ups, were passed into either the left or the right side of the heart in dogs. In some animals, complete heart block was produced by surgical or pharmacologic means. This provided an opportunity to study the effect of varying P-R intervals on the auricular contribution to the first sound and on summation gallops.

Two distinct components of the intracardiac fourth sound were recorded. The first consisted of a short, low frequency vibration 0.06 second after the P wave. The second component was a prolonged, higher frequency series of vibrations occurring 0.08-0.12 second later. At times, this second component was of sufficient duration to appear as an atrial systolic murmur. During short P-R intervals, the second component of the atrial sound was obscured as it fused with the initial vibrations of the first sound complex, but with A-V dissociation it was clearly demonstrated.

The fourth sound recorded in the right ventricle was frequently louder than that in the right atrium, lending support to the theory that vibrations of ventricular walls play an important role in the production of the atrial sound.

Effect of Human Fibrinolysin (Plasmin) upon Deep Thrombophlebitis in Man: A Controlled Study

Kenneth M. Moser, George C. Hajjar, and Stephen B. Sulavik, Washington, D.C.

In theory, the combination of an effective thrombolytic agent with anticoagulant drugs would represent an optimum medical regimen for the management of acute thrombotic disorders.

Previous uncontrolled studies have suggested that intravenous administration of human fibrinolysin (plasmin) within a dosage range acceptable from the viewpoint of toxicity will favorably alter the course of acute deep thrombophlebitis in man. The present report deals with clinical results obtained in 2 comparable groups of patients with deep thrombophlebitis of less than 10 days' duration. One group (30 patients) was treated with anticoagulant drugs alone; the other (32 patients), with fibrinolysin plus anticoagulant drugs.

Results were as follows (average values in days from start of therapy): In those receiving anticoagulant drugs alone, pain resolved in 8.1 days; edema in 6.9; normal extremity size returned in 7.2; ambulation was permitted in 10.8; and the total hospital stay was 19.4. During the period

of hospitalization, 4 patients had pulmonary embolism (1 fatal), 2 had phlebitic recurrences, and 2 left the hospital with post-phlebitic residuals. In the receiving combined fibrinolytic-anticoagulant therapy, pain resolved in 4.6 days; edema in 4.6; normal extremity size returned in 4.8; ambulation was permitted in 7.7; and total hospital stay was 14.8. During hospitalization, 1 nonfatal embolus occurred, and no recurrences were observed. Two patients left the hospital with post-phlebitic residuals.

The results suggest that a combined fibrinolytic-anticoagulant regimen leads to more rapid resolution of the acute phlebitic episode than anticoagulant drugs alone and may reduce the early incidence of phlebitic recurrence and pulmonary embolization.

Alterations in the QRS Complex Produced by Atrial and Ventricular Paroxysmal Tachycardias in the Presence of Bundle-Branch Block Pattern: An Experimental Study in Dogs

Otto F. Muller,^{*} Philadelphia, Pa., Manuel Cardenas, Mexico City, Mexico, and Samuel Bellet, Philadelphia, Pa.

Bisteni and co-workers (1957) studied the configuration of extrasystoles induced electrically at various portions of the cardiac cycle in normal sinus rhythm and bundle-branch block. The purpose of the following investigation was to determine the variation in the QRS complexes of atrial and ventricular tachycardias induced by acetylcholine, after experimental production of partial and complete bundle-branch blocks. The following observations were made:

1. Supraventricular tachycardias do not alter complete bundle-branch block patterns significantly; they may, however, increase the QRS width of incomplete types of bundle-branch block.
2. The QRS morphology of ventricular tachycardias from the ventricle below the affected bundle depends upon the portion of the cardiac cycle in which the stimuli fall. Stimulation between the T wave and the beginning of P produces complete bundle-branch block patterns of the contralateral type. Stimuli which fall within the P-R interval fuse with the activation wave coming from the atrium through the unaffected branch and result in narrowed or relatively normal QRS complexes. Fusion beats can be seen which exhibit the typical morphology of the V-P-W syndrome if the ventricular stimulus is discharged immediately after the P wave.

Similar multiform ventricular extrasystoles were observed during cardiac catheterization in patients with complete right bundle-branch block when the catheter tip encroached on the right ventricular endocardium and produced runs of paroxysmal ventricular tachycardias.

These findings are of help in explaining the variations in the QRS width and configuration that occasionally occur with ventricular tachycardias in the presence of bundle-branch block patterns.

Effects of Bromsulphalein and Saline Infusions on Hepatic Hemodynamics in the Dog

John F. Murray and Ismael Mena, Los Angeles, Calif.

Three hepatic hemodynamic parameters were studied in 16 dogs: (1) all animals had pressures measured from the inferior vena cava (IVCP) and portal vein (PVP) or wedged hepatic vein (WHVP), giving the pressure gradient across the liver (Δ HP); (2) external scintillation counting over the heart and liver to determine cardiac output and cardioportal circulation time (8 dogs); and (3) hepatic blood flow (HBF) measured by the indicator-dilution technique (12 dogs).

Direct PVP, but not WHVP, measurements showed a 0.5-1.0 cm. H₂O, transient fall in Δ HP 20-30 seconds after single, intravenous injections of bromsulphalein (BSP 5 mg. per Kg.). This decline was usually followed by a prolonged Δ HP increase of 1-3 cm. H₂O over control values apparent from both PVP and WHVP studies.

After the BSP prime in 12 animals, sustaining infusions of 0.15 mg. per Kg. per minute (2 ml. per minute) caused a further increase of Δ HP and a later rise in IVCP. This response was partly due to the fluid administered because comparable amounts of saline alone caused a similar but less marked rise of PVP, IVCP, and Δ HP.

When the PVP was increased, external scintillation counting over the liver showed consistently delayed peak radioactivity time compared to control tracings at lower pressures. There was no change in cardiac output. HBF did not change following single BSP injections but decreased in most sustained infusion studies.

The rise in hepatic vascular resistance depends upon the amount of BSP and volume of fluid used; these factors should be controlled in all hemodynamic liver studies.

Dicumarol Therapy, Platelet Clumping and Clotting Tests

J. F. Mustard and E. A. Murphy, Toronto, Canada

Intravascular clumping of platelets is the first stage in the formation of thrombi. Early animal experiments on Dicumarol therapy showed that whenever thrombus formation was effectively prevented the onset of platelet clumping was also considerably prolonged. Quick commented in 1944 that for rational use of Dicumarol, an exact

study correlating the prothrombin time with the inhibition of platelet clumping was necessary. Since it has been shown that the prothrombin time does not measure that aspect of clotting associated with platelet clumping, it is important that this question be answered.

Therefore, 30 patients receiving Dicumarol and related drugs were studied. Platelet clumping was measured, using a modification of tests described by Mills and Sharp. The prothrombin time, clotting time, plasma (PTC) activity in thromboplastin generation and platelet adhesiveness were studied and their correlations with platelet clumping examined.

These studies showed that adequate anticoagulant therapy makes platelets less adhesive and delays clumping. Of the other tests used the clotting time gave the best correlation with change in platelet clumping; the prothrombin time gave a poorer correlation. The clotting time was a reliable index of platelet clumping in all subjects; the prothrombin time was as good an index in approximately a quarter of the subjects, fair in half, and poor in the remainder.

A further observation was that the same prothrombin time corresponded to different degrees of change in platelet clumping from patient to patient. Although spontaneous hemorrhage occurred in some patients with prothrombin times as low as 30 to 35 seconds, the onset of platelet clumping had been prolonged to more than 10 times normal in all instances.

Therefore, since platelet clumping is important in both thrombosis and hemostasis, the findings from this study may explain in part discrepancies and difficulties encountered in anticoagulant therapy regulated solely by prothrombin times.

Pulmonary Hypertension in Children with Systemic-Pulmonary Communications

Alexander S. Nadas, Abraham M. Rudolph,[†] and Julien I. E. Hoffman, Boston, Mass.

The presence or absence of pulmonary hypertension in children with septal defects and patent ductus arteriosus is of paramount importance. In many instances it reflects the severity of the lesion, determines the prognosis, and influences in large measure the success of operative correction. Over 200 patients with ventricular septal defect, over 100 individuals with patent ductus arteriosus and secundum atrial septal defect respectively, and over 50 patients with atrial septal defect primum lesions were studied by cardiac catheterization and the data analyzed in terms of flows, pressures, and resistances.

The review of this material indicates that in children with ventricular defect about 30 per cent

have pulmonary arterial mean pressure of over 40 mm. Hg, whereas in atrial septal defect primum 15 per cent, and in atrial septal defect secundum less than 10 per cent fall into this category. It seems evident that this ratio in all 3 groups remains constant throughout childhood. There seems to be a tendency, however, among those with ventricular septal defect and pulmonary hypertension to show higher values in the latter part of childhood than in infancy. Repeat studies in more than 25 children with ventricular defects performed at 1 to 8 year intervals fail to show progression of pulmonary hypertension in any instance. That this relative stability in the pulmonary arterial pressure is not the dominant pattern of adult life is suggested by our figures on patients with secundum-type atrial septal defects.

It is our opinion, based on the data obtained so far, that pulmonary arterial hypertension and pulmonary vascular obstruction do not develop throughout childhood although progression of established vascular disease may occur in rare instances.

Effects of Acute Arterial Blood pH Changes on Catecholamine Plasma Levels, O₂ Uptake and Circulatory Adaptations

Gabriel G. Nahas, J. C. Ligou, and Benjamin Mehlman, Washington, D.C.

In the course of acute hypercapnia induced in the dog, plasma catecholamine levels measured by the method of Weil-Malherbe and Bone rise from 0-1.5 $\mu\text{g. per L.}$ to 8-12 $\mu\text{g. per L.}$, as arterial blood pH falls to 7.20. With a greater fall in pH, plasma catecholamines increase further, reaching 84-92 $\mu\text{g. per L.}$ when pH is 6.60.

Under these conditions of hypercapnia and high catecholamine plasma levels associated with normal blood oxygenation, the following circulatory changes are first observed: increase in mean blood pressure, cerebral vasodilatation and kidney ischemia. In addition, O₂ consumption is significantly depressed. When pH falls below 6.90, the depressant effect of acidosis prevails and a circulatory collapse is observed in the presence of very high catecholamine plasma levels; cardiac endocardial and myocardial lesions are observed in the animals which die in these conditions. Such lesions are identical with those produced by parenteral administration of catecholamines. When an organic CO₂ buffer 2-amino 2-(hydroxymethyl)-1,3 propanediol or THAM is administered intravenously, it is possible to re-establish pH to its normal level and at the same time restore all the circulatory disturbances to normal and bring plasma catecholamine back to control levels, where

producing a marked increase in oxygen consumption. These findings suggest that catecholamine administration, under clinical conditions of circulatory failure associated with low blood pH, is of questionable value.

Influence of Cholinergic Drugs upon the Coronary Flow Changes Induced by Epinephrine in Dogs

Clinton B. Nash and Robert A. Woodbury, Memphis, Tenn.

The blocking action of pilocarpine and other cholinergic drugs on the systemic vasodepressor response of epinephrine following adrenergic blockade has been previously reported. In this study dogs anesthetized with barbiturates were placed on artificial respiration and the heart exposed. Coronary blood flow changes were estimated from flow measurements made by a Shipley-Wilson rotameter interposed in the circumflex branch of the left coronary artery. Control injections of 0.5 μ g. of epinephrine and norepinephrine into the coronary artery produced definite increases in blood flow with minimal heart rate and blood pressure changes. This flow increase was blocked or reduced by pilocarpine. This influence of pilocarpine upon coronary blood flow changes induced by epinephrine was reversible by atropine.

Thorax Model Studies of the Effect of the Blood Inside the Heart on the Electrocardiogram

Clifford V. Nelson,[†] Manu Chatterjee, and William H. Austin, Portland, Me.

Previous studies have indicated that the intracardiac blood significantly influences the recorded electrocardiogram and that the magnitude of the effect depends on the direction of the electrical excitation vector relative to the cavity wall. Further tests have been made by means of dog bladders suspended in a thorax-model electrolytic tank. Limb and circumferential chest leads have been measured with an artificial dipole tangential, radial to, and at intermediate angles with the bladder. Five fluids, having resistivity values, varying from 130 to 1,100 ohm-cm., were perfused through the bladder, representing limiting conditions for the blood-filled cavity and the homogeneous thorax. Recorded potentials were standardized to values for a dipole moment of 1.0 n.-cm.

With tangential dipoles, low resistivity fluid (blood) generally reduced potentials by amounts up to 50 per cent, depending on the lead position. Radial dipole potentials were generally increased by a similar amount, and with oblique dipoles,

the potentials were increased in some regions and decreased in others.

Changing the fluid resistivity altered the lead potentials by amounts up to 2 mv., and in some cases produced polarity changes. In spite of changes in limb lead amplitudes, the calculated Einthoven angles were usually not changed by more than 10°, although in some cases changes of 30°, or more, were noted.

These data indicate that the intracardiac blood must be considered in any attempt to quantitate a heart vector. We have found, in addition, that the magnitude of the effect is inversely related to the distance of the center of an excitation dipole from the cavity.

Clinical Use of the Pump-Oxygenator without Donor Blood for Priming or Support during Extracorporeal Perfusion

Wilford B. Neptune, Frederick G. Panico, and James A. Bougas, Boston, Mass.

There are many pump-oxygenators being used successfully. They have as a common disadvantage the requirement of large volumes of blood for priming. Donor blood for priming presents added difficulties beyond obtaining and processing donors. There are problems of storage and blood waste. More important, as the number of blood units increase, there is an increased risk from mismatching, reactions, abnormal bleeding, acidosis, and late sequelae, such as serum hepatitis.

We are using a bubble-type oxygenator which has been modified for our present technique. We no longer use any donor blood for priming. Our perfusions have varied from 15 minutes to over 1 hour and the flow rates have been in the range of 65 to 80 ml. per Kg. per minute.

The only blood which the patient receives is ordinary A.C.D. blood to cover blood loss and pleural drainage in the postoperative period. In perfusions under 30 minutes we use from 1 to 2 units of A.C.D. blood during surgery and in perfusions up to 1 hour we have needed from 3 to 4 units of blood; 1 unit has usually been sufficient to cover pleural drainage in the postoperative period.

Selected patients with various ages, body weights, perfusion times and cardiac lesions will be presented. In general, the average patient having an open heart procedure has received less blood than the average patient having a lung resection. Moreover, this is ordinary bank blood which eliminates or minimizes many problems with previous techniques. Extensive physiologic monitoring and blood chemical studies have been done and no adverse effects have been demon-

strated. Based on an experience with 20 cases, the technic would appear safe, practical, and feasible.

Practical Considerations in Long-Term Anticoagulant Therapy to Prevent Myocardial Infarction

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During 15 years, 667 patients, aged 35 to 90 years, received anticoagulants to prevent myocardial infarction for periods ranging up to 13 years. Cerebral vascular insufficiency or infarction was present in 42. The prothrombin time was maintained at twice normal value in seconds. Other clotting factors were registered. After 2 years, the interval of testing was often monthly in "stable" patients. Hypertension rarely precluded therapy. Hemorrhage was rarely serious. Liver toxicity was unrevealed in clinical studies in 200 cases and in 77 necropsies. Recurrent infarctions and deaths were halved in comparison with patients not persevering with the regimen. Most recurrences developed when prothrombin time was less than twice normal.

One phenindione and 6 dicoumarin derivatives were freely interchanged for evaluation with occasional erratic responses. The prothrombin time seemed best regulated with phenindione, acenocoumarol, warfarin sodium, or phenprocoumon.

Clinicians unfamiliar with the vagaries of anticoagulant effects during shifting clinical states should know that dosage should be reduced when antibiotics, salicylates, nicotinic acid and monamine oxidase inhibitors are prescribed or when hepatic congestion, renal malfunction, adherence to a rigid low-fat or low-protein diet, or excessive alcohol intake is encountered.

Increment in dosage is necessitated when anginal pain is accelerated, during excessive dehydration or increased intake of dietary protein and fat (including unsaturated fatty acid proprietary preparations), or after blood transfusions.

Anticoagulants should be tapered off to avoid thromboembolism within a matter of days or weeks after sudden discontinuance. Prolonged coagulation during surgery and dental extractions is far preferable to hypercoagulability.

Clinical and Hemodynamic Studies of 50 Patients with Transposition of the Great Arteries

Jacqueline A. Noonan, Alexander S. Nadas, and Abraham M. Rudolph,† Boston, Mass.

Detailed physiologic data regarding pressures and flows in the pulmonary and systemic circulations, and the level and directions of shunts are

necessary for understanding the complex hemodynamics of transposition of the great arteries. Our clinical and cardiac catheterization studies in 50 patients with proven transposition of the great arteries, ranging in age from 11 days to 11 years, indicate that these individuals do not form a homogeneous group.

We have divided the patients into 2 major categories. Fourteen patients with an intact ventricular septum form group I and 36 with a ventricular defect comprise group II. The latter is subdivided into 3 groups. Group IIA consists of 11 patients with pulmonic stenosis (defined as a gradient of 50 mm. or more across the pulmonary valve and a low pulmonary artery pressure). Group IIB is formed by 13 patients with pulmonary vascular obstruction (Rp of 4 mm. Hg per minute per M.² or greater). Group IIC is comprised of 12 patients with a large pulmonary blood flow and normal pulmonary resistance (Rp of 3 units or less).

The clinical picture particularly the electrocardiogram and x-ray as well as the prognosis and surgical implications vary for each group. Severe anoxia from inadequate shunting with early death is common in group I while group IIC, with a relatively higher oxygen saturation die in congestive failure from the large pulmonary blood flow. Groups IIA and IIB have smaller pulmonary blood flows from obstruction at either the valvular or arteriolar level and in general have a better prognosis.

Studies on Salvage of Infarcted Heart Muscle by Fibrinolytic (Plasmin) Therapy

Irwin Nydick, Paul Rueggsegger, Ramon Abarquez, Claude Bouvier, Robert V. Hutter, Eugene E. Clifton, and John S. LaDue, New York, N.Y.

We have previously demonstrated the dissolution of experimental coronary thrombi by the administration of fibrinolysin (plasmin) with reduction of microscopic evidence of edema, congestion, and capillary thrombi in early infarction. The present study was designed to assay the therapeutic effect of fibrinolytic therapy upon the evolution and extent of myocardial infarction at intervals up to 14 days following temporary coronary occlusion.

The left anterior descending coronary artery was clamped in dogs during thoracotomy and released 3 hours after chest closure. Twenty control and 25 treated animals were studied. Fibrinolytic activity (euglobulin method) of less than 1 hour lysis time was induced in the treated animals by intravenous plasmin. The infusion was started

1 hour before and continued for 4 hours after release of the clamp. The animals were sacrificed 1 to 41 days after infarction. The treated hearts showed 25 to 50 per cent smaller, often spotty infarcts, usually localized to the apical and subendocardial region, whereas infarction in the control hearts was transmural, involving the entire anterior wall. Microscopically, the untreated hearts showed frequent microthrombi and confluent areas of necrosis, while the treated hearts showed no microthrombi, and necrosis was often spotty and less extensive.

These results appear to show that the viability of myocardium deprived of its blood supply may be much longer under the conditions of these experiments than the often-quoted 30 minutes. Furthermore, dissolution of capillary microthrombi by fibrinolysis may be just as important as the lysis of thrombi in the larger branches of the coronary arteries.

Elasticity in Isolated Strips of Human Aorta

Robert W. Oblath, Balakrishna Hegde, Leslie Kaeburn, and George C. Griffith, Los Angeles, Calif.

Information about the character of the aortic wall is necessary for the design of adequate substitute materials. To obtain information as to the viscoelastic properties of aortic tissue and changes therein in health and disease, longitudinal and transverse specimens from the ascending aorta, aortic arch, thoracic aorta, and abdominal aorta were obtained from 91 human cadavers, stripped of adventitial tissue, and studied by means of a specially constructed sensitive elastometer developed in the electronics laboratory of the University of Southern California School of Medicine.

With both a transverse and longitudinal section taken from each of 4 areas of the aorta, a maximum of 182 sections were available from each area. Sections from the thoracic area of the aorta were most amenable to study with the elastometer; 55 per cent (99) of the sections from the abdominal aorta were too brittle to permit study.

Measurements of hysteresis obtained from hypertensive patients in this study contrast sharply with values obtained from atherosclerotic individuals: in 6 of the 8 aortic areas sampled, tissues from hypertensive individuals demonstrated even less hysteresis than the average for the entire, unselected group of patients; average values for aortic segments from atherosclerotic individuals showed greater hysteresis than averages of the unselected group.

Experimental Employment of a Nonionic Detergent as a Method of Reducing Fat Embolization Resulting from Mechanical Cardiopulmonary Bypass

Guy Owens, Jesse E. Adams, James R. Headrick, Anthony Munoz, and H. William Scott, Nashville, Tenn.

We have previously reported clinical and experimental studies which demonstrated severe systemic fat embolization following prolonged cardiopulmonary bypass. These studies, conducted with filming and macrobubble oxygenators, indicated that the coalescence of fat into emboli is related to the oxygenating process rather than to the type of propelling force employed. Because these oxygenators are characterized by a direct contact of blood with gas, it was speculated that an alteration of surface tension forces might be responsible. In an effort to prevent this alteration, a nonionic detergent (pluronic) was selected for this experiment.

In a group of 10 adult mongrel dogs, complete cardiopulmonary bypass was maintained for 2 hours, employing a stationary screen oxygenator. Biopsies of various organs, and blood and urine specimens were obtained immediately before and after bypass. All biopsies were stained with Sudan IV to demonstrate fat emboli in the tissues. The detergent, in doses of 0.6 mg./ml. blood was employed in five dogs, while the remaining dogs served as controls.

Tissue specimens obtained from those animals that had received pluronic demonstrated a significant reduction of fat emboli as compared with the control series.

Reduction in Serum Cholesterol Levels and Other Metabolic Effects of Large Doses of Nicotinic Acid

William B. Parsons, Jr., Madison, Wis.

Large oral doses of nicotinic acid (3 to 10 Gm. daily) administered to more than 60 hypercholesteremic patients for periods up to 3 years have reduced serum cholesterol levels to normal in the majority of patients. The reduction is most prominent in the β -lipoprotein cholesterol fraction with reduction in the beta/alpha₁-lipoprotein cholesterol ratio. Flushing, which usually occurs only in the first week of therapy, can often be reduced by use of modified nicotinic acid preparations. Upper gastrointestinal irritation or aggravation of peptic ulcer can be eliminated by use of buffered nicotinic acid.

Impaired glucose tolerance occurs in many patients, but frank diabetes has appeared infrequently and disappears when nicotinic acid therapy is discontinued. In most instances, the newly

acquired diabetes can be controlled by diet while therapy with nicotinic acid is continued.

Serum uric acid levels are increased during nicotinic acid therapy (more than 6 mg. per cent in 29 of 40 patients) but neither gouty arthritis nor urinary calculi have been observed.

Liver dysfunction, evidenced by increased BSP retention, has occurred in a minority of patients (6 of 49 patients after 1 to 3 years of therapy) but thus far has not been accompanied by consistent morphologic abnormality in needle biopsy specimens.

All these metabolic changes are readily reversed following cessation of therapy with nicotinic acid, which also permits cholesterol levels to return to the pretreatment range. Intravenous injection of nicotinic acid results in *in vivo* production of fibrinolysin in many individuals. Studies relating to this phenomenon are being reported elsewhere. Nicotinamide, which fails to reduce serum lipid levels, also fails to produce fibrinolysin following parenteral injection.

Incidence of Arrhythmias in Chronic Cor Pulmonale

Bernard H. Pastor, Philadelphia, Pa., and Leo J. Corazza, Hazleton, Pa.

Cardiac arrhythmias have generally been considered rare in chronic cor pulmonale and it has even been suggested that their occurrence strongly suggests the coexistence of another type of heart disease. The observation of frequent, persistent, and troublesome arrhythmias in patients with chronic pulmonary disease at the Philadelphia Veterans Administration Hospital prompted a review of these cases. Of 122 patients with chronic cor pulmonale but no clinical, electrocardiographic or pathologic evidence of any other etiologic type of heart disease, 47 patients (31 per cent) had 1 or more arrhythmias, a total of 62 being observed in the group. Very irregular, bizarre atrial arrhythmias, with beats arising in multiple foci, have been encountered which appear to be quite characteristic. The high prevalence of arrhythmias can readily be explained on theoretical grounds. In 37 cases (59.7 per cent) the arrhythmias coincided with the development of pulmonary infection with its accompanying bronchospasm, hypoxia, and hypercapnia. Digitalis was a factor in only 15 of the arrhythmias and 7 of these coincided with the onset of infection also, suggesting that this may have sensitized the patients to the toxic effects of digitalis. Associated coronary artery disease does not seem to have been a factor in the production of arrhythmias as has been suggested by other workers, and in our experience severe coronary atherosclerosis is rare in patients with cor pulmonale.

Choice of an Anticoagulant

Bernard H. Pastor, Theodore Rodman, and Robert W. Smith, Philadelphia, Pa.

The prothrombinopenic agents are most widely used in clinical anticoagulant therapy because of their low cost and ease of administration, despite the theoretically greater efficacy of heparin. Because of the technical difficulty of maintaining smooth control of anticoagulant therapy many new drugs have been introduced since bishydroxycoumarin (Dicumarol) was first used in 1942. Many clinical studies have suggested a marked superiority of one or another of these newer agents over the parent drug, but these studies have generally been poorly controlled. A comparative study was made of 6 commonly used prothrombinopenic drugs, bishydroxycoumarin, warfarin (prothromadin) phenindione (Hedulin), diphenadione (Dipaxin), acenocoumarin (Sintrom) and anisindione (Miradon), administered concurrently under comparable conditions and in comparable dosage to 450 patients. Using an induction schedule consisting of a large single loading dose and a small maintenance dose on the following day, 82 per cent of the patients could safely be brought into the therapeutic range of 10 to 30 per cent prothrombin activity within 40 hours. Differences in induction time, ease of maintenance and stability of maintenance dose among the drugs were not sufficiently great to recommend one drug over another, and the majority of patients can be well controlled with any of the drugs studied. It was also demonstrated that satisfactory control can be achieved with prothrombin time determinations 3 times weekly after a stable therapeutic level is reached. The incidence of major hemorrhage was 2 per cent, of minor hemorrhage 6 per cent, apparently unrelated to the drug employed.

Mechanical Properties of the Pulmonary Artery

Dali J. Patel, Donald P. Schilder, Alexander J. Mallos; and with the technical assistance of Alfred G. T. Casper, Bethesda, Md.

The mechanical properties of the pulmonary artery are important determinants of pulmonary hemodynamics, particularly if instantaneous pulmonary artery flow is to be computed from the pulmonary artery pressure and its spatial gradient. It is the purpose of this report to describe the relationship between the instantaneous distending pressure and diameter of the pulmonary artery in 15 living thoracotomized dogs. This relationship was studied over a range of pressures during control periods and norepinephrine administration.

Results indicate: 1. The pulse contours of pulmonary artery pressure and diameter are essentially identical, indicating negligible inertance and viscous resistance of the vessel wall. 2. Mean change in average radius during a cardiac cycle was ± 7 per cent, ± 2.6 S.D., ± 0.7 S.E.M. (5 per cent per cm. H₂O pulse pressure) under control conditions. 3. The ratio of change in radius to pulse pressure ($\Delta r/\Delta p$) at comparable pressures showed a significant decrease during norepinephrine administration when compared to control ($p < .01$). Elastic diagrams constructed from these data showed that for a given stretch the vessel wall developed a greater circumferential tension during norepinephrine administration. These results suggest that norepinephrine increased vessel wall stiffness. 4. Contrary to general belief, cross sectional area of main pulmonary artery exceeded that of right and left combined. 5. An electrical caliper with adequate recording characteristics was developed for instantaneous diameter measurement.

These results indicate that a relatively simple pressure-diameter relationship exists which may be used in the measurement of instantaneous pulmonary artery blood flow and in evaluation of various pharmacologic agents.

Physiologic Extracorporeal Circulation Based on Continuous Monitoring of Blood Gas Tensions

Bruce C. Paton, Vernon Montgomery,^{*} and Henry Swan, Denver, Colo.

The physiologic theories underlying oxygenators have been subjected to experimental scrutiny. The principles thus outlined have been applied successfully to the control of clinical perfusions.

Using 2 rotating disc oxygenators experimentally in a closed circuit with O₂ and CO₂ passing through one and N and CO₂ through the other, the relationships between pump and disc speeds, gas flow rates and concentrations, arterial and venous oxygen tensions, and pH have been determined; the similarity between such an oxygenator and a person breathing only O₂ and CO₂ has been demonstrated.

The adequacy of a perfusion is best judged by the continuous measurement of arterial and venous oxygen tensions, the arteriovenous oxygen difference and arterial pH. In order to measure the blood pO₂ continuously autoclavable polarographs have been designed. These electrodes give instantaneous readings, minimally affected by changes in temperature and flow rates at the O₂ tension involved. The pH is measured by a Beckman Zeromatic meter. Using the information available, appropriate changes are made in pump and disc speeds to maintain an arterial pO₂ of

90-115 mm. Hg and a venous pO₂ of 35-45 mm. Hg. The pH is controlled here by the admixture of 2-4 per cent CO₂ with the oxygen and by changing the total gas flow rate. Adequate oxygenation can be attained with gas flows of 2-4 L. per minute, but at these low rates increasing concentrations of CO₂ in the oxygenator decrease the pH.

Figures from more than 50 clinical perfusions have been prepared.

Circulation in Induced Acute Head Injury

John L. Patterson, Jr., Richmond, Va., Joseph T. Doyle, Albany, N.Y., David W. Richardson, Sami I. Said, and Edith L. Hardie, Richmond, Va.

Circulatory and respiratory responses to severe cranial injury inflicted by a sledge hammer have been studied during the processing of 12 unanesthetized cows (*Bos taurus*) in the abattoir.

Immediately following a blow sufficient to render the animal comatose, respiration ceased. In 6 animals there was gradual and irregular return of breathing after about 1 minute, while in the rest apnea was permanent. Heart rate rose to approximately 160 beats per minute. Carotid, pulmonary arterial and right atrial pressures also rose, the carotid strikingly (peak level 320/192 mm. Hg). With return of respiration, pressures stabilized near control levels, whereas with permanent apnea, arterial pressures remained normal or elevated until a gradual decline developed after 10 to 12 minutes. Cardiac output doubled in 1 animal within the first minute after a single blow to the head and, in another fell to 45 per cent of control 2 minutes after 2 hammer blows. The electrocardiogram showed an immediate sinus tachycardia and in some animals RS-T segment depression and terminal T wave inversion in right ventricular-type leads. Later, there were increasing degrees of A-V heart block with progressively slower idioventricular rhythm. Arterial pO₂ fell to an extreme of 15 mm. Hg and pCO₂ rose to over 115 mm. Hg.

The results demonstrate that in these animals, respiration was the function critically affected. It appears that, in the early postinjury period, the brain must recover from the concussion sufficiently to reinstitute breathing or be rapidly and irreversibly trapped by the falling arterial O₂ and rising CO₂ tensions.

Long-Term Clinical and Physiologic Effects of Aortic-Pulmonary Anastomosis in Tetralogy of Fallot

Milton H. Paul, Robert A. Miller, and Willis J. Potts, Chicago, Ill.

Twenty-one patients who had aortic-pulmonary anastomoses performed before 1949 were examined to evaluate their present clinical status. Twenty of these patients also had catheterization studies to evaluate pulmonary artery pressures, pulmonary vascular resistances, and intracardiac shunts. This group represents a sample of a more complete analysis in progress on the first 100 patients who had aorticopulmonary anastomoses performed approximately 10 years ago.

Of these 21 patients, 13 were considered to have a good, stable, 10 year postoperative status and 5 young adults in this group are extremely active. Three patients have fair results with slight limitation on normal activities. Five patients have a poor 10 year result with progressive symptoms, including chest pain, dyspnea, and syncope.

At catheterization the pulmonary artery was entered in 15 patients and 7 had mean pulmonary artery pressures less than 20 mm. Hg, 6 had pressures between 20 and 30 mm. Hg, and 2 had pressures of 45 and 75 mm. Hg. The estimated pulmonary vascular resistance was below 3 resistance units in 12 patients. Resting arterial oxygen saturation was below 80 per cent in 3 patients, between 80 and 90 per cent in 8 patients and above 90 per cent in 9 patients. A left-to-right shunt was demonstrated at the pulmonary artery level in 13 patients; however, in 6 of these there was also significant arterialization of right ventricular samples.

Review of the initial operative procedure and postoperative course 10 years ago indicates that 3 of the 5 patients with long term poor results had too large an initial aorticopulmonary communication with early postoperative cardiomegaly and congestive failure. Each of these patients at present has recurrent chest pain, absence of a continuous murmur, and marked aneurysmal dilatation of the pulmonary arteries.

Hospital Acquired Bacterial Endocarditis

Morton L. Pearce, Lucien B. Guze, Los Angeles, Calif., and Leonard Staugus, Santa Monica, Calif.

Clinical, laboratory, and autopsy data from 85 cases of bacterial endocarditis were coded onto IBM cards. Bivariate distributions of various parameters were determined employing an IBM 101 statistical machine. The hospital acquired group of 17 cases was found to differ considerably from the 68 cases in the nonhospital acquired group. These differences included: 1. The patients with hospital acquired infection were all 46 years old or older. 2. Only 7 of the 17 were recognized

during life. Most of the other 10 patients received antibiotics for various reasons which may have obscured the diagnosis. 3. Fourteen of 17 patients had major surgery and 12 had urological instrumentation such as catheterization or cystoscopy. 4. There were 9 staphylococcal infections; there was cultural identification of the organism in 5 cases. 5. Fourteen of 17 patients died during hospitalization. Only 1 of the 3 survivors was alive at 1 year follow-up. 6. Although the distribution of valve involvement of the 14 autopsied cases in the hospital acquired group was similar to the nonhospital acquired group, the incidence of involvement of previously normal valves was much higher (11 of 14), and the incidence of valve perforation was much lower (2 of 11) than in the nonhospital-acquired group.

Contribution of the Lungs to the Electrocardiogram of Cor Pulmonale

Morton L. Pearce and Leonard Haber, Los Angeles, Calif.

This study is directed toward a separation of cardiac and thoracic factors in the electrocardiogram (ECG) and vectorecardiogram (VCG) of cor pulmonale. The ECG diagnosis of right ventricular hypertrophy (RVH) secondary to congenital heart disease or rheumatic heart disease rests on fairly dependable criteria. These criteria are not satisfactory for the diagnosis of RVH secondary to lung disease until the RVH becomes marked.

To establish more precisely the anatomic definition of RVH, individual chamber volumes and weights and weight ratios were established in 170 cases in which ECG's were available for correlation studies. Cases with left ventricular hypertrophy, infarction or extensive myocardial fibrosis were excluded, leaving 30 for this study.

1. Cases with RVH without lung or thoracic disease: The results are similar to those reported.

2. Cases with lung and/or thoracic disease. With no or minimal RVH there is a diminution in lateral voltage, here defined as RV_6 one half or less of SV_1 . This change is secondary to an altered volume conductor. With moderate RVH the QRS axis becomes vertically or rightward as well as posteriorly directed. This is also seen in VCG's employing orthogonal leads. In advanced RVH the QRS axis becomes anterior as well as rightward directed as is seen in RVH due to other causes.

3. The appearance of "P pulmonale" failed to correlate with right atrial weights or volume. It correlated best with the degree of RVH.

Blood Flow and Oxygen Tension in the Vasodilated Skin

Raymond Penneys, Philadelphia, Pa.

Skin oxygen tension in the moderately vasodilated fingers was compared with that in the fully vasodilated fingers to see whether the large increment in blood flow with full vasodilatation was accompanied by a comparable increase in oxygen. Moderate vasodilatation was obtained in normal subjects by allowing them to lie covered with blankets, except for the hands which were left exposed, in a constant temperature room with an air temperature of 20 C. Full vasodilatation was produced by the addition of heating pads to the body. The skin temperature of the finger tips at moderate vasodilatation averaged 29.9 C. and at full vasodilatation, 31.5 C. This indicates an increase in blood flow of some 50 per cent in passing from the moderately to the fully vasodilated state. (Plethysmography is now being included as a more definitive measurement of blood flow.) Skin oxygen tension was measured with the open-tip polarographic oxygen electrode, inserted in the finger pads. Oxygen tension of the skin (11 experiments on 7 subjects, 3 or 4 fingers per experiment) increased only 5 per cent, in spite of the 50 per cent increase in blood flow, on passing from moderate to full vasodilatation. The large increments in flow with full vasodilatation, therefore, serve primarily not to bring in additional oxygen, but more likely to assist in the regulation of body temperature.

Some Interrelationships Between Oxygen and Carbon Monoxide Diffusing Capacities and Pulmonary Hemodynamics

Peter Perkins,* Herbert Constantine, Frank W. Lorejoy, Jr., and Paul N. Yu, Rochester, N.Y.

DLO₂ and single breath DLCO were measured in 30 patients. The DLO₂ was determined in conjunction with right heart catheterization and radioisotope dilution studies.

The patients were grouped thus: (1) chronic pulmonary disease, (2) compensated valvular heart disease, (3) decompensated valvular heart disease, and (4) congenital heart disease with increased pulmonary blood flow (PBF).

In a given patient, DLCO was almost always greater than DLO₂, both at rest and during exercise, although the differences in mean values were statistically significant only in groups 1 and 3.

With exercise, there was a significant increase in both mean DLO₂ and mean DLCO in all 4 groups. Both at rest and during exercise no statistically significant difference of DLCO was observed be-

tween any 2 groups. However, DLO₂ was significantly greater in groups 2 and 4 than in group 1, and also greater in group 4 than in group 3.

During exercise, there was usually a parallel increase in DLO₂ and PBF in patients of groups 1 and 2, whereas the changes were slight in group 3 and variable in group 4. No correlation was found between the changes in the pulmonary blood volume and DLO₂ during exercise. In patients of group 3, a significant increase in total pulmonary resistance was associated with relatively small increase in DLO₂ during exercise.

These observations suggest that the increase in DLO₂ with exercise is proportional to PBF and inversely related to the total pulmonary resistance, but not to the pulmonary blood volume.

Clinical Recognition of Tricuspid Stenosis

Joseph K. Perloff and W. Proctor Harvey, Washington, D.C.

In 12 proven cases of tricuspid stenosis, the majority relatively early in their course, clinical features and their mechanisms were studied. Bed-side recognition, achieved in 11 instances, depended principally upon physical signs. The murmur of tricuspid stenosis differed from its mitral counterpart by selective intensity increase during inspiration. Intracardiac phonocardiography recorded the murmur with this respiratory characteristic in right ventricle but not in right atrium, localizing it at the tricuspid valve. Stenosis impeded inspiratory augmentation of right ventricular filling, consequently simultaneous right atrial-right ventricular pressures showed an inspiratory increase in tricuspid gradient. Since orifice size remains constant, inspiration should therefore cause increased transvalvular flow rate with increased intensity of tricuspid stenotic murmur. Simultaneous left atrial-left ventricular pulses showed the mitral stenotic gradient uninfluenced by respiration, resulting in no inspiratory accentuation of mitral stenotic murmur. Normal splitting of the second sound occurred only twice. Tricuspid opening snap was recorded twice but was heard in neither case.

Right atrial contraction against a stenotic valve generated large, often giant, jugular *a* waves followed by shallow *v* waves and gentle *y* descents due to attenuated right atrioventricular flow rate. This jugular pulse contour, unassociated with physical, electrocardiographic, or radiologic signs of right ventricular hypertension strongly suggests tricuspid stenosis. Its availability was attested by the presence of sinus rhythm in 10 cases. In atrial fibrillation *a* waves disappeared, *v* waves rose, but the gentle *y* descents persisted.

In this study, clinical criteria were evaluated which should permit frequent early recognition of tricuspid stenosis.

Hourly Variation in Total Serum Cholesterol

John E. Peterson, Alan A. Wilcox, Melvin I. Haley, Loma Linda, Calif., and Robert A. Keith, Claremont, Calif.

During the course of previous studies in a group of 44 healthy male medical students, we were impressed by the remarkable lability of serum cholesterol in certain of our subjects. Changes amounting to more than 200 mg. per cent were observed in a few individuals from one morning to the next. From this group of 44 students, 5 subjects, whose serum cholesterol had been quite labile during the period of semester examinations, were selected for some additional study. These 5 students were hospitalized for 5 days, and venous blood samples were obtained from an indwelling polyethylene catheter at intervals ranging from 1 to 4 hours. Total cholesterol was measured by the method of Pearson, Stern, and McGavaek, and all determinations were run in duplicate.

On control days when the subjects were undisturbed, the changes in serum cholesterol from hour to hour were found to be quite moderate. On other days, however, when a mildly stressful experience was introduced we observed a remarkable lability. Changes amounting to as much as 100 mg. per cent were found to occur within a period of 4 hours.

Similar studies also were conducted with a group of 5 students whose serum cholesterol levels previously had shown relatively little change during the period of semester examinations. In contrast with the labile subjects, these persons showed a much more stable hourly pattern throughout the experiment. The difference in these 2 groups was particularly evident on days when some stressful experience was introduced.

These studies add support to the view that individuals may differ greatly in regard to the lability of serum cholesterol. They also indicate that remarkable changes may occur from hour to hour in certain individuals and that such lability may be induced by situations which would appear to be only mildly stressful in nature.

Mixing, Segmental Velocity and Regurgitation in Indicator-Dilution Curves

Arthur O. Phinney, Jr., Hartford, Conn., Keith Cotton, Sidney, Australia, and John Shillingford, London, England

An analysis of factors altering the dye-dilution curve in valvular regurgitation has been made

in a model circulation. The model was designed to study large atrial volume, low flow circuits such as those found clinically with mixed lesions of the mitral valve. Two specific effects of regurgitation were identified. One was to increase the mixing of dye particles in the "atrium" with a resultant increase in the spread of the indicator dilution curve. Similar effects were produced in the model by mixing with a rotating paddle inserted into the atrium. Regurgitation had no significant effect on the spread of the curve if the dye was already well mixed before reaching the mitral valve.

The second effect was to increase the velocity of flow through a segment of the circuit centering around the incompetent valve, without influencing the rate of transit of "the altered dye bolus" past the sampling site. This was a velocity increase relative to the flow occurring through a competent valve of the same diastolic dimension using the same aortic flow, and was produced by the greater diastolic flow per unit time from atrium to ventricle as the valve became more and more incompetent. It resulted in a shortening of the appearance time of the curve.

By analyzing these 2 effects, the ratio of the spread of the curve to the appearance time proved to be an easy and useful index of regurgitation in the range of forward output and volume used in these experiments.

Preparation of Electrocardiographic Data for Processing and Analysis by Digital Computer

Hubert V. Pipberger, Edward D. Freis, Leonard Taback, and Henry L. Mason, Washington, D.C.

Analog records such as the electrocardiogram have to be converted into numerical, i.e., digital, form before processing through digital computers. A pilot facility for automatic analog-to-digital data conversion has been assembled.

Three orthogonal electrocardiographic leads (Schmitt's SVEC III system) were recorded simultaneously on magnetic tape through frequency modulation channels. Using the playback mechanism these signals become available as voltages. They are displayed simultaneously on an oscilloscope screen by means of an electronic switch. After selection of a cardiac cycle for conversion a "record" switch is pressed to start the automatic equipment. The 3 leads are sampled 1,000 times per second, and the digital information is transmitted to "write" electronics for re-recording on digital magnetic tape. The tape format was chosen for an IBM 704 digital computer.

The reliability of the data conversion equipment is tested by plotting the electrocardiograms from the numerical print-out obtained from the computer. They compared with the original records within 1 per cent error. More than 300 cases have been processed.

Once the electrocardiogram is obtained in digital form, further processing merely requires writing suitable instructions for the computer. A great variety of completely objective analytic procedures are being applied, such as measurement of spatial magnitude and orientation curves with their rate of change, planarity of spatial QRS and T loops and others. The high speed of computer data processing lends itself to large-scale statistical studies and mass-screening programs.

Use of Precordial Recording in Studies Involving the Dilution Principles

Walter H. Pritchard, William J. MacIntyre, Thomas W. Moir, and Frank H. Gott, Cleveland, Ohio

An accurate estimation of cardiac output by the dilution principle is possible in human subjects by precordial counting following the intravenous injection of iodinated (I^{131}) serum albumin. Although the best results have been obtained by viewing predominantly either the right or left heart, counter placement is not critical if the following conditions are met: (1) the volume viewed in the inscription of both the primary curve and the final diluting level is essentially the same; (2) the final extrapolated curve is derived primarily from the final clearing chamber; and (3) the intravenous injection is sufficiently rapid to insure sharply delineated concentration peaks and clearance slopes. In human subjects, a correlation study of this method with an arterial puncture technic has shown satisfactory agreement, with an average deviation of ± 9 per cent in 34 runs studied.

With suitable positioning of the precordial counter, double peaked curves representative of the right and left heart can be obtained. From these curves, the mean transit time of passage of the indicator from right to left heart can be calculated, and the circulating central blood volume estimated by the Stewart-Hamilton formula. The anatomic boundaries of this volume are the lungs and left heart. In normal subjects the average value of this volume is estimated to be about 25 per cent of the total blood volume.

The precordial counting technic has also proved useful in demonstrating the presence of left-to-right, intracardiac shunts in congenital heart

disease. Characteristically, delay in the clearance slopes of the precordial curves are indicative of such lesions.

Significance of Upright T Waves in Right Precordial Leads in Infants and Children

William L. Proudft and Fernando A. Tapia, Cleveland, Ohio

Upright T waves in right precordial leads in children may be seen in right ventricular hypertrophy but may also occur as a result of reciprocal changes in left ventricular hypertrophy. Two groups of cases were studied: 1 was an unselected group consisting of cases in which the T waves were upright in right precordial leads, and the other was a group in which there was an anatomic lesion causing pure left ventricular hypertrophy (coarctation or aortic stenosis). In the absence of electrocardiographic evidence of left ventricular hypertrophy, upright T waves in right precordial leads in children under the age of 12 years were associated with evidence of right ventricular hypertrophy in every case except 1, in which the right ventricle was hypoplastic in association with tricuspid atresia, atrial and ventricular septal defects and patent ductus arteriosus. Frequently upright T waves occurred before the development of other evidence of right ventricular hypertrophy. Usually the degree of right ventricular hypertension was mild or moderate. When S-T segment depression and T wave changes of left ventricular hypertrophy were encountered, upright T waves occurred in the absence of right ventricular hypertrophy.

In the group of patients in which pure left ventricular hypertrophy was present, when S-T segment depression and T waves changes occurred in V_5 and V_6 , about half had upright T waves in right precordial leads in association with reciprocal elevation of the S-T segments.

Variations of Serum Lipids in Vegetarian and Non-vegetarian Males

Carroll B. Quinlan, J. Gordon Barrow, Gerald R. Cooper, Virginia S. Whitner, and Mary Helen R. Goodloe, Atlanta, Ga.

Dietary studies of Trappist vegetarian and Benedictine nonvegetarian monks indicate that they differ significantly ($p < .001$) in their percentage of calories from fat (Trappists: 25 per cent; Benedictines: 45 per cent).

Variations in serum lipids have been noted between the 2 communities, between age groups in the same community, between individual monks in the same age group and in the same individual

at different times. Comparing the vegetarians with nonvegetarians, most serum lipids are significantly lower ($p < .001$) in the former group. In both communities, serum lipids rise until about age 60, when a decline is noted. It appears that this rise with age, therefore, is independent of the relative level of fat intake. In addition, this rise cannot be attributed to differences in fat intake within the community, since each age group consumes a similar quantity of fat. Marked variations in serum lipids have been noted between monks within the same age group who are apparently eating the same diet. These variations, therefore, are not related, either to age or percentage of calories from fat. Finally, it has been observed that in some monks, the serum lipid concentrations have been rather constant in blood samples drawn at different times of the year, while others have revealed a marked intra-individual variation.

The magnitude and significance of these observations have been evaluated along with possible factors which might explain these variations.

Role of Catecholamines in the Origin of Stress-Induced Myocardial Necroses

Wilhelm Raab, Ernest Stark, and Wilda R. Gige, Burlington, Vt.

In discussing the production of myocardial necroses by various types of stress in corticoid-sensitized animals, Selye raised the question as to what metabolic factor these "unspecific" stresses might have in common.

Practically all types of stress are accompanied by liberation of potentially necrotizing catecholamines (Cannon's "emergency reaction"). Considering the initiating role of reflectory sympathoadrenal catecholamine discharges in the stress syndrome, their causal involvement in the stress-induced cardiac necrotizations was suspected. An attempt was made to break the chain of events by administering drugs which inhibit catecholamine liberation, either through ganglionic blockade or catecholamine depletion.

Forty rats were pretreated with 2- α -methyl-9- α -fluorohydrocortisone for 7 days and then restrained on a board for 15 hours. Part of the animals received daily doses of Serpasil for the same period, others received Inversine shortly before restraint. Histologic examinations were done "blindly." Sixty-five per cent of the controls displayed severe (grade III) necroses, and only 10 per cent had none. None of the drug-treated rats had grade III necroses; 40 per cent were entirely normal. Average severity grades were 2.4 for the controls and 0.8 each for the Serpasil- and Inversine-protected animals.

The stress-induced catecholamine accumulations in the rat heart (Raab), the prevention of cardiac necrotization by section of the reflex-mediating cervical cord (Selye) and the marked protective effect of ganglionic blockade and of Serpasil suggest a fundamental causal involvement of metabolic catecholamine action in the origin of stress-induced myocardial damage.

Use of Gas Chromatography in Detection and Location of Left-to-Right Shunts in Man

Lloyd H. Ramsey and C. Gordon Sell, Nashville, Tenn.

The ability to separate and analyze, quantitatively, the N_2O in 1 ml. samples of whole blood, irrespective of the nitrogen content, with great sensitivity, accuracy and rapidity by the use of gas chromatography, was applied to the problem of detection and localization of left to right shunts during right heart catheterization of man. With a catheter in the pulmonary artery and an indwelling needle in a systemic artery, 2 ml. samples of blood were obtained anaerobically between the fourth and eighth seconds, following a single deep breath of 100 per cent N_2O . The samples were analyzed immediately for their N_2O content in a Beckman GC-2 Gas Chromatograph. No N_2O was present in the pulmonary artery in this time interval in normal patients.

In 17 patients (aged 1½-46 years) with left-to-right shunts at atrial or ventricular level, N_2O was detectable in the 4-8 second sample obtained from the pulmonary artery, in amounts of .08 to 4 vol. per cent. Systemic arterial samples contained N_2O in amounts from 5 to 20 vol. per cent at the same time. O_2 saturation samples, obtained from 4 of the 17 patients with shunts, did not reveal the presence of the shunt. Localization of the shunt was determined by withdrawing the catheter to proximal chambers and repeating the test when N_2O was found to be present abnormally in the pulmonary artery.

The simplicity, rapid analysis time (less than 5 minutes), and the ease of analysis, make the use of N_2O and gas chromatography a method of shunt detection and localization of great practical value.

"Straight Back" Syndrome

Maurice S. Rawlings, Chattanooga, Tenn.

A new syndrome of heart disease, apparently due to a previously unrecognized chest deformity, is introduced. Nine cases have been collected in 3 years. In this deformity, the normal curve of the upper dorsal spine becomes straightened so that the examiner's flattened palm may be superimposed

tion on the area without deviation of the extended fingers.

This "straight back" syndrome may produce pseudo heart disease in 1 of 2 ways. First, as in tunneling of the sternum, there is a decrease in the AP diameter of the chest which may compress the mediastinal structures and cause false heart enlargement in the frontal view, particularly in the great vessel area. This is due to a relative inward displacement of the straightened dorsal spine. The condition is easily recognized when lateral views are taken. Secondly, in cases of severe mediastinal compression, the defect may be associated with the production of mechanical murmurs. These murmurs are systolic in timing, usually basal in location and would seem related to impingement or distortion of the great vessels. Rarely is the defect found without either false heart enlargement or mechanical murmurs.

These defects are simple and may not be uncommon. Recognition of this condition may prevent a common form of iatrogenic heart "disease" that could be excluding many patients from employment, insurance or peace of mind.

Spread of the Excitation Wave in the Ovine Left Ventricle

Richard W. Redding, Charles R. Smith, and Robert L. Hamlin, Columbus, Ohio

The objectives of the investigation were to determine the mean spatial vector forces of the ovine heart and the process of excitation of the left ventricle.

Analysis of standard limb leads, chest leads, and vectorcardiograms revealed that the mean spatial QRS forces consisted of 2 major vectors. The first is directed posteriorly and to the right or left. The second, and largest, vector force runs in the anterior, dorsal and right or left direction. The mean spatial vectors are different from those reported for the dog and man.

Epicardial electrograms of the left ventricle consist of rS deflections at the apex, QS on the anterior, free and posterior wall and Rs on the base. The epicardial surface, except for the base, faces the electronegative portion of the activation process. Two reasons are suggested: (1) activation progresses from the epicardium toward the endocardium; (2) activation of the musculature occurs almost synchronously.

Endocardial electrograms are similar to epicardial leads. Simultaneous endocardial and epicardial electrograms reveal an exceptionally small time differential at the onset of the intrinsic deflections. Serial intramural electrograms at 2 mm. levels are QS deflections throughout the left ventricular free wall. The time of onset of the in-

trinsic deflection in the intramural leads is almost synchronous throughout. The distribution of the ovine Purkinje system is markedly different from that of the dog. The findings of the experiment and the anatomic distribution of the Purkinje system suggest an instantaneous multifocal mechanism of spread of the excitation wave.

Effects of Prolonged Periods of Hypothermically Induced Cardiac Arrest on the Isolated Perfused Guinea Pig Heart

S. Frank Redo, New York, N.Y.

Isolated guinea pig hearts were subjected to cardioplegia using hypothermia. Amplitudes of contraction and electrocardiograms were recorded. Periods of arrest were from 10 to 180 minutes. Mechanical and electrical arrest, with rare exceptions, occurred simultaneously, at temperatures from 14-17 C. Initial electrical recovery occurred at about the same temperature as the mechanical recovery or, in some instances, a fraction of a second sooner. Initial recovery was manifest at temperatures of 21 to 25 C. Maximum mechanical recovery, as measured by the amplitude of contraction, returned to 25-90 per cent of the initial amplitude of contraction, while the rate usually returned to that which preceded the cardioplegia. In general, the longer the period of arrest, the smaller was the amplitude of contraction at the time of maximum recovery.

The electrocardiogram at the time of maximum recovery was essentially the same as that taken at the control time, prior to beginning hypothermia, except for a decrease in the voltage of the atrial and ventricular complexes. In no instance did the heart fibrillate when reheating was started.

Maximum recovery, both electrical and mechanical, occurred when temperature had returned to 38 C. The results indicate that the isolated perfused guinea pig heart does not tolerate prolonged periods of hypothermic arrest well. Although electrical activity returns to a pre-arrest pattern, except for slightly decreased voltage, the mechanical activity does not return to control levels. These factors lead to the conclusion that prolonged periods of arrest achieved in this fashion lead to myocardial damage that prevents return of function to that of control levels.

Mechanism of the Antiarrhythmic Effects of Sympathomimetic Agents

Timothy J. Regan, Kenan Binak, Berton L. London, and Harper K. Hellem, Detroit, Mich.

The capacity of vasopressor agents to revert ventricular arrhythmias has been ascribed to a

change in coronary dynamics or a direct myocardial effect. The possibility that this effect may be mediated through altered ion transfers has been tested by obtaining paired samples of arterial and coronary sinus blood for potassium and sodium analyses to assess their net movements.

Ventricular arrhythmias have been regularly produced by rapid injection of acetylthiocholine (0.05 mg. per Kg.) in 8 intact vagotomized dogs, inducing an abrupt movement of K^+ from the myocardium for a 10 minute period, independent of blood flow or heart rate. Planimetric integration of A-V difference areas, before and after the drug, indicated a net negative area of 1.14 square inch ($p < 0.001$).

The rapid administration of adrenaline (1 μ g. per Kg.) was attended by a biphasic response, with initial K^+ uptake. To utilize this uptake phase, 3 μ g. per Kg. of adrenaline was infused during the initial 6 minutes of strophanthidin activity in 7 dogs. Ventricular arrhythmias were totally prevented and the expected K^+ egress was blocked. Planimetric integration indicated a net positive area of 1.1 square inch. Since hypertension from aortic clamping did not change K^+ A-V in 5 dogs, the pressor response itself would not account for these ion changes. Preliminary experience with methoxamine has indicated an activity altogether similar to that of adrenaline, but at least 3 mg. per Kg. were needed to prevent the arrhythmias and K^+ egress.

Since the efficacy of these agents is related to blockade of K^+ egress, as previously found true of Pronestyl, a direct action on myocardial ionic content would appear to account for their anti-arrhythmic property.

Experimental Study on the Origin of T Waves Based on Determinations of the Effective Refractory Period from the Epicardial and Endocardial Aspects of the Ventricle

Ernest W. Reynolds, Jr., and Condon R. Vander Ark, Ann Arbor, Mich.

Present knowledge of the order of transmural recovery is based largely on observations of the behavior of surface T waves in known pathologic states. There are few studies which include direct measurements of the order of recovery across the ventricular wall. Using the principle that the refractory period parallels the course of recovery as measured by the T wave or the membrane action potential, the authors have found in 31 paired observations that there were small differences in the time in which surface units completed recovery compared with subendocardial units. This appeared to be correlated with the polarity of the

T wave. When surface T waves were negative, the epicardium recovered an average of 11.2 msec. later than the subendocardium, and when the surface T waves were positive surface units recovered 8 msec. in advance of the deeper layers. Such small differences in recovery time suggest that all units from the endocardium to the epicardium recover during the same period of time, except for the final rapid phase of recovery.

Additional measurements made after ligating a branch of the left anterior descending coronary artery during the acute ischemic phase associated with tall positive T waves and elevation of the RS-T junction, show a consistent acceleration of recovery at the subendocardial layer (mean reduction -24.4 msec.). This finding is in harmony with Trautwein's observation that the membrane action potential is shortened when cells are exposed to low oxygen tension fluids.

Clinical and Hemodynamic Effects of a New Antihypertensive Drug

David W. Richardson, Eugene M. Wyso, Joseph H. Magee, and Gordon C. Cavell, Richmond, Va.

A newly developed antihypertensive agent, 2-octahydro-1-azocinyl-ethyl guanidine (Ciba SU-5864), has been shown by Maxwell, Mull, and Plummer to produce long-lasting inhibition of response to electric stimulation of sympathetic nerves in animals, without producing ganglionic blockage or reducing responses to injected norepinephrine. It is presumed to prevent release of norepinephrine from sympathetic nerve endings.

Twenty-three hospitalized male patients, with severe hypertension, who received 25 to 400 mg. of the drug daily for periods from 5 days to 2 months, developed striking reduction in blood pressure, beginning 48 hours following onset of treatment and lasting 4-14 days after the drug was stopped. Diastolic pressure, for example, decreased on an average of 23 mm. Hg supine and 45 mm. Hg standing. Pressures fell more markedly in the standing than lying position and pulse pressure decreased.

Cardiac output, measured by indicator dilution, fell together with the fall in blood pressure; peripheral resistance stayed unchanged. Orthostatic reduction in renal plasma flow (C_{PAH}) and glomerular filtration (C_{In}) was exaggerated during drug administration, as compared with pretreatment values. Undesirable effects included orthostatic hypotension, which prevented reduction in supine pressures to normal levels, mild diarrhea and infrequent nausea.

SU-5864 is a potent antihypertensive drug with a novel pharmacologic action. Absence of de-

case in total peripheral resistance or in renal vascular resistance, together with orthostatic hypotension and reduction in pulse pressure during administration of the drug, suggest that it reduces blood pressure by pooling blood in peripheral vessels, rather than by arteriolar dilation.

Adherence to a Prudent Diet and its Effectiveness in Lowering Serum Cholesterol: Study of 97 Free-Living Normal-Weight Men, Aged 50 to 59

Seymour H. Rinzler, Morton Archer, and Norman Jolliffe, New York, N.Y.

By April 30, 1959, 97 free-living normal-weight men, aged 50-59, had completed at least 6 months on a "prudent" diet pattern: calories 2,000-2,700, protein 130-150 Gm., carbohydrates 250-280 Gm., and fats 66-97 (30-33 per cent of calories). The diets were composed of approximately equal proportions of saturated, monounsaturated and polyunsaturated fatty acids.

This group represented 91 per cent of the 107 men who had been placed on this diet. The hypocholesterolemic effect of the diet is measured by the drop in the average "benchmark" (control) serum cholesterol level from 253 to 225 mg. per cent after 6 months. When the group is distributed into previously established thirds on the basis of their benchmark cholesterol values, the upper third (34 men with benchmarks 270 mg. per cent or more) fell from 298 to 253; the middle third (32 men with benchmarks 230 to 269 mg. per cent) fell from 249 to 224; the lower third (31 men with benchmarks under 230 mg. per cent) fell from 207 to 191—falls of 15, 10 and 8 per cent, respectively, and all statistically significant beyond the .01 level. The average weight was 156 pounds initially and 154 pounds after 6 months on this diet.

Of these men, 54 had completed at least 1 year on the diet. The average benchmark level of this group was 255 mg. per cent; 224 after 6 months and 227 after 12 months on the diet. In men with prior coronary heart disease, the cholesterol levels fell similarly to others with the same benchmark levels.

Treatment of Stokes-Adams Attacks in Heart Block, with Special Reference to Parenteral, Sublingual and Long-Acting Isoproterenol

Stanley R. Robbin and Simon Dack, New York, N.Y.

The treatment of Stokes-Adams attacks in complete heart block was evaluated in 15 cases. The procedure included: 1. Emergency administration of intramuscular or sublingual isoproterenol.

2. Continuous intravenous drip of isoproterenol, beginning with concentration of 2 mg. per 500 ml. and increasing if necessary to 10 mg. per 500 ml. at 20-40 drops per minute. 3. Gradual weaning from isoproterenol by progressively reducing the dose and rate of flow and switching to intermittent intramuscular and sublingual administration. 4. The use of the artificial electrical pacemaker if isoproterenol is ineffective. 5. Maintenance therapy with sublingual and long-acting ingested tablets of isoproterenol (30 mg.).

A technic has been developed for continuous intravenous isoproterenol administration which has proved to be lifesaving in 10 of the cases. The dose and rate of administration must be titrated and regulated by continuous ECG monitoring and the artificial pacemaker must be continuously attached for emergency use if ventricular standstill occurs. In 3 cases, a high concentration of 10 mg. (50 ampules) per 500 ml. water administered at the rate of 40-60 drops per minute for long periods was necessary to maintain an adequate ventricular response. Other patients were more sensitive to isoproterenol and smaller doses were required to avoid too great an increase in the sinoauricular rate. Beyond a critical rate (120 per min.) fatigue of the A-V bundle and ventricular standstill may develop. This applied to the sublingual tablets also.

In 12 of the patients, observations were made on the use of long-acting tablets containing 30 mg. isoproterenol for maintenance and prophylaxis. In several cases it proved to be an effective agent. It provided more constant and prolonged effect on heart rate and obviated the need of taking sublingual tablets at frequent intervals, particularly during the night.

Ten-Year Cure of Malignant Hypertension by Removal of a Goldblatt Kidney, Demonstrated by an Aortogram

Joseph T. Roberts, Buffalo, N.Y.

A young man with nearly fatal malignant hypertension was shown, by injecting Diodrast into the renal arteries, to have a defective blood supply of the left kidney. A catheter, placed through the femoral artery into the aorta, was used. Intravenous and retrograde pyelograms were not abnormal. Blood pressure fell in a few minutes after temporarily closing the affected renal artery, although grossly the kidney seemed normal. Since removal of the partially ischemic kidney 10 years ago, his blood pressure has remained normal, his lost vision has returned, and the bilaterally detached retina, papilledema, hemorrhages and exudates have returned to normal. The renal lesion

was a proliferative nodular, layered thrombus with tearing of the arterial layers of the renal artery, giving about 80 per cent occlusion of the renal artery. Aortography and even operative search for the occasional Goldblatt-type of hypertension seems advisable, especially in relatively young patients with malignant, progressive hypertension. Hazards of aortography must be evaluated against the risk of the disease. Hypertension due to unilateral renal ischemia is rare; in 10 years we have found only 5 other less dramatically cured cases. When present, however, treatment of this highly specific type of hypertension may give gratifying results.

Endocarditis and Hydrodynamics

Simon Rodbard, Buffalo, N.Y.

Our analysis of pathologic findings suggests that endocarditis occurs only at sites of high velocity blood flow. Thus, high pressure gradients extruding blood through narrow orifices produce lesions on ventricular surfaces of insufficient aortic valves, on atrial surfaces in mitral insufficiency, and beyond narrowings of coarctations and arteriovenous fistulae. Initial vascular injury is not a prerequisite. Endocarditis does not occur in large openings, as at atrial septal defects or widely patent ductus, since high velocities are not produced. High velocity flow produces its effects because it reduces lateral pressure locally, eliminates normal perfusion from lumen to intima, and can cause retrograde perfusion of intima by oxygen-poor, substrate-poor, and metabolite-rich fluids from the media. Oxygen, substrates, antibiotics, etc., therefore, cannot enter the site even though they are present in abundance in the immediately adjacent arterial blood. This interpretation is supported by animal experiments showing increased lipid infiltration above an induced stenosis and absence of infiltration at the narrowing, and by experiments on deformable tubes. Stream velocity also affects growth and distribution of bacteria, as shown in *in vitro* experiments. High velocity jets tend to erode the lip of the narrowing, producing local deformity and distant embolization; closure of the narrowing and elimination of the jet may "cure" the lesion. These considerations suggest that hydrodynamic factors determine special characteristics of endocarditis.

Involvement of the Heart by Bronchogenic Carcinoma: A Clinical Pathologic Study

Theodore Rodman, Melvin Sobel, and Bernard H. Pastor, Philadelphia, Pa.

Studies of autopsy material have indicated that bronchogenic carcinoma frequently invades the

heart. Clinicians, however, seldom observe cardiac symptoms or signs which they attribute to tumor involvement. In order to assess the clinical importance of cardiac involvement by bronchogenic carcinoma, we have reviewed our clinical and autopsy experience with lung cancer during the past 6 years at the Philadelphia Veterans Administration Hospital. The records of 275 patients with histologically proved bronchogenic carcinoma were studied. Two hundred and thirty-one of the patients died in the Philadelphia Veterans Administration Hospital. Autopsy was performed on 201 or 87 per cent of the patients.

The heart was involved by tumor in 48 per cent of the patients on whom autopsies were done. In 23 patients (11 per cent of the autopsied group) cardiac involvement by tumor was the primary cause of death. In another 34 patients (17 per cent of the autopsied group) cardiac involvement appeared to contribute importantly to the patient's death. The pericardium was involved most frequently and tamponade was the most frequent single cause of cardiac death.

The antemortem manifestations of tumor invasion of the heart encountered most frequently were pericardial friction rubs, supraventricular tachycardias (most commonly atrial flutter), and S-T segment and T wave changes suggestive of pericarditis. Changes in the roentgenologic appearance of the heart were not often observed.

Electropolarographic Method for Evaluation of the Effect of Cardiac Revascularization Procedures

Lloyd S. Rogers and Francis Caliva, Syracuse, N.Y.

There is general agreement that an accurate, reproducible physiologic method for evaluation of cardiac revascularization procedures is needed. The electropolarograph permits such evaluation. When platinum electrodes of an electropolarograph are placed in the myocardium of a dog, they record a marked and rapid rise in tissue oxygen with oxygen breathing, if any effective circulation to the area exists. They record no such response in a totally ischemic area.

A 6 channel electropolarograph has been constructed. Its 6 electrodes are used simultaneously to measure the size of the totally ischemic area produced by temporary occlusion of a branch of the anterior descending coronary artery in dogs. The exact position of each electrode and the site of artery occlusion are accurately marked and the revascularization procedure under study is performed. At a second operation after any desired time interval, the oxygen response of the identical area of myocardium is recorded after occlusion of the coronary artery at the same site used in the original measurement. Any effective collateral

circulation produced by the revascularization procedure will become evident by a response to oxygen breathing at 1 or more electrodes which did not respond to such stimulation before the procedure. The applicability of this method to internal mammary ligation and the Beck type of operation has been investigated.

Phonocardiography in the Diagnosis of Patent Ductus Arteriosus

William M. Rogers, James R. Malm, James S. Harrison, George H. Humphreys, II, and Antonio Demetz, New York, N.Y.

Adequate diagnostic criteria were obtained from phonocardiograms in 60 uncomplicated cases of patent ductus arteriosus. In the present study, we sought information useful in evaluating an atypical ductus. Since direct phonocardiography with simultaneous pressures and an electrocardiogram have proven an effective means of analyzing valvular lesions and septal defects, we applied the same method to 20 patients at the time of surgical closure of a patent ductus.

The most informative records were obtained from the pulmonary artery. The murmur characteristically late in its onset, with a pause after the first sound crescendos to a maximum after the peak in the aortic pressure tracings and decreases throughout diastole. In a typical ductus, this maximal turbulence engulfs the second heart sound. With a small shunt, the normal sequence of aortic and pulmonary valve closure is documented by the dirotic notch in the aortic pressure curve occurring before the notch in the pulmonary tracing. This produces a normal split second sound. In large shunts, the greater volume ejected by the left ventricle prolongs systole, delays aortic valve closure and its dirotic notch. Corresponding reduction in volume, ejected by the right ventricle, shortens systole, advances pulmonary valve closure and its associated dirotic notch. Thus, the pulmonary component of a split second sound precedes the aortic. Normal splitting of the second sound increases with inspiration. Reversed splitting increases with expiration. The dirotic notch of carotid pulse tracings identifies aortic closure. A return to normal follows ductus ligation. Experimental and clinical cases illustrate the above.

Association of a Specific Overt Behavior Pattern in Women with Increased Blood Cholesterol and Clotting Time, Arcus Senilis, and Incidence of Clinical Coronary Disease

Ray H. Rosenman and Meyer Friedman, San Francisco, Calif.

The possible role of socioeconomic pressures in the pathogenesis of clinical coronary disease was studied in 3 volunteer groups of women (aged 30 to 60 years) chosen by lay selectors solely on the basis of different overt behavior patterns. Group A women (69) exhibited a behavior pattern characterized by sustained, competitive "drive," ambition, and constant immersion in occupational "deadlines." Group B women (103) conversely exhibited complete absence of "drive," and freedom from occupational "deadlines." Group C women (85) also exhibited no "drive," but were variously subject to moderate occupational "deadlines."

In each instance blood cholesterol, lipoproteins, clotting time, habitus and maternal-menstrual and family history data were obtained; dietary, smoking, drinking, and exercise habits were precisely assayed, and presence of arcus senilis and clinical coronary disease were determined.

Women in group A exhibited markedly higher average blood cholesterol (294 mg./100 ml.) and incidence of arcus senilis (35 per cent) and clinical coronary disease (36 per cent) than women in group B (216 mg./100 ml., 8 and 7 per cent respectively) or group C (255 mg./100 ml., 25 and 7 per cent respectively). Clotting times were fastest in group A women.

These striking differences were not ascribable to differences in caloric or fat intake, age, habitus, or "femininity." Thus, a specific behavior pattern in women was associated with elevated blood cholesterol, faster clotting time, and higher incidence of arcus senilis. The findings also suggest that this behavior pattern plays an important causal role in inducing clinical coronary disease in women, as we previously found in men.

Vectorcardiographic Analysis of Myocardial Infarction Characterized by Tall R Waves in Right Precordial Leads

Edwin L. Rothfeld, Fred W. Wachtel, William S. Karlen, and Arthur Bernstein, Newark, N. J.

Employing the cube reference system, vectorcardiograms were obtained in 6 cases of myocardial infarction that displayed prominent R waves in right precordial leads. In all cases, the initial portion of the QRSsE-loop was displaced markedly to the right and anterior and showed bizarreness of contour and delay in inscription. This unusual finding was ascribed to a loss of electrical forces directed to the left and posterior resulting from direct posterolateral wall myocardial infarction.

The vectorcardiogram is of major diagnostic import in confirming the diagnosis of postero-

lateral myocardial infarction and in differentiating it from other causes of prominent R waves in right precordial leads, such as right ventricular hypertrophy and right bundle-branch block.

Acute Effects of Cigarette Smoking on Pulmonary Function Studies

Edwin L. Rothfeld, Newark, N.J., David Biber, Union, N.J., and Arthur Bernstein, Newark, N.J.

Pulmonary function studies were performed on a group of 42 smokers, including 23 with varying types and severity of lung disease and 19 normals. These studies were then repeated immediately after smoking 1 or 2 cigarettes. There was no significant change in vital capacity, timed vital capacity, maximal breathing capacity or functional residual capacity. However, a significant and striking increase in the ventilation equivalent, expressed as liters of air breathed per 100 ml. oxygen consumption, after smoking was observed as compared with a control group. In most cases, this rise in ventilation equivalent was due to hyperventilation associated with a minimal to moderate decrease in oxygen consumption. No significant differences were noted between patients with pulmonary disease and normals.

It is suggested that the inefficient respiratory mechanism caused by cigarette smoking may be related to the chronic pulmonary disorders associated with this habit.

Effect of Nicotine on Muscle Blood Flow in Man

Hans Rottenstein, Carlisle, Pa., George Peirce, Philadelphia, Pa., Ellier Russ, Bordentown, N.J., David J. Felder, Trenton, N.J., and Hugh Montgomery, Philadelphia, Pa.

It has been known for many years that the injection of nicotine, and usually the smoking of tobacco, cause cutaneous vasoconstriction. With moderate doses there is a small increase in pulse rate and in blood pressure. As far as we know there has been no previous direct measurement of the effect of nicotine on blood flow in human skeletal muscle. Our main method of measurement was by venous occlusion plethysmograph combined with skin-blanching by adrenalin iontophoresis. The Hensel thermoelectric needle was employed in some instances. When both methods were used the needle was placed in one calf, the plethysmograph on the other. Distal to the plethysmograph the circulation of the foot was largely excluded by cuff-pressure. At times some difficulties were encountered with the Hensel needle, and the data from its use are reported

only when it responded in a typical fashion to arterial compression and to adrenalin administered intravenously. Changes in cutaneous flow in toes were estimated by skin temperatures in a 20 C. room. Nicotine was administered intravenously in a single dose of 1 to 2 mg. in 1 minute or of 3 mg. in 4 minutes. The cutaneous flow decreased, and by both methods of measurement the muscle blood flow increased; this increase was for a shorter period than was that of the decrease in cutaneous flow.

Pulmonary Wedge Position as a Site for Injection of Indicator-Dilution Substances

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A small left-to-right shunt may be difficult to detect by oximetry or by routine indicator dilution curves when the injection is done into the right-sided cardiac chambers or the pulmonary artery. However, if the indicator is injected while the catheter is in the pulmonary wedge position, a sharper curve is produced which has a shorter appearance, build-up and disappearance times. Shunts which could not be detected on the indicator-dilution curves from other sites may become apparent, or those which were doubtful previously may become clear-cut. It is believed that the sharper curve and the clarification of the shunt is due to: (1) the smaller "central volume," diluting a wedge injection; (2) the shunting of a somewhat higher concentration of indicator so that the recirculation curve is sharper, hence more clearly defined. This modification may, in some cases, eliminate the necessity for alternative procedures of simultaneous use of 2 cardiac catheters or left-heart injection.

Effects of Changes of Pulmonary Blood Flow, Pulmonary Arterial and Pulmonary Venous Pressure on Pulmonary Vascular Resistance in Normal and Serotonin-Constricted Vessels

Abraham M. Rudolph† and Peter A. M. Auld, Boston, Mass.

The degree of constriction of the pulmonary vasculature has been assessed widely as the basis of calculated pulmonary vascular resistance, using the formula:

$$\frac{\text{Pulm. arterial mean} - \text{Pulm. venous mean pressure}}{\text{Pulmonary blood flow}}$$

In order to evaluate the effects of changes in each of these factors, the pulmonary circulation was perfused separately from the systemic cir-

ulation in open-chest intact dogs. Systemic oxygenation was maintained with a rotating disc or bubble oxygenator. Pulmonary blood flow, pulmonary venous pressure and pulmonary arterial pressure could be varied over a wide range; 1 of these factors could be kept constant while the other 2 were modified.

An increase in pulmonary blood flow resulted in a decrease of pulmonary vascular resistance. At high flows, the calculated resistance in the serotonin-constricted vessels could be reduced to levels considered normal at lower flows for normal vasculature. Increase in pulmonary venous pressure produced a marked reduction of pulmonary vascular resistance. The effect was most marked at lower pulmonary venous pressures. At levels of 15-20 mm. Hg in the normal vasculature, further increase in pulmonary venous pressure produced no further significant change in resistance. In the serotonin-constricted vasculature, the effects of pulmonary venous pressure changes were even more marked, and decreases in resistance were produced up to pulmonary venous pressure levels of 25-30 mm. Hg.

Increases in pulmonary arterial pressure also produced a decrease in resistance, but the effects were not as striking as with changes in pulmonary venous pressure.

These data suggest that the usual formula for calculating resistance assesses only impedance to flow but does not provide information regarding elasticity of the vessel or vascular tone.

Factors Influencing Gallop Rhythm

Arthur Ruskin and Bob Gerner, Galveston, Tex.

The effects of decreased and increased cardiac inflow and of vasoconstrictor and vasodilator drugs were studied in 21 cardiac patients with gallop rhythm. Simultaneous electrocardiograms (lead II) and stethograms were recorded at constant loudness in the aortic, pulmonic, tricuspid and mitral areas in the horizontal and vertical positions.

Standing consistently decreased the amplitude of the gallop sound, with variable effects on the 2 primary heart sounds. Tourniquets (50 mm. Hg, 4 extremities, 5 minute) likewise decreased the gallop sounds in both the horizontal and vertical posture in all areas. More often than not, the first 2 heart sounds also decreased in loudness; occasionally, however, they appeared louder, especially in the vertical position. Mecamylamine (Inversine, 1.5 mg., I.M.) usually decreased the gallop sound record, corresponding to the nadir

in the venous and arterial pressures. The primary heart sounds, on the other hand, often increased in recorded loudness, especially in the vertical position. Phenylephrine (Neosynephrine, 5-10 mg. I.M.) consistently increased the loudness of the gallop, as well as of the 2 heart sounds, in all areas, as measured at the height of the arterial and venous pressures. Exercise (varying with the state of the patient) and 50 per cent glucose (50 ml. I.V.) gave surprisingly variable effects.

In summary, pooling of blood away from the thorax decreased the amplitude of the gallop, though not necessarily the other heart sounds. Global vasoconstriction, increasing the central blood volume, made the heart and gallop sounds louder.

Evaluation of Combined Therapy, Utilizing Thyroxin, Thyroid Extract, and Vitamin B Factors in the Treatment of Angina Pectoris

Henry I. Russek, Staten Island, N.Y.

To assess the effects of thyroid therapy in patients with coronary artery disease, this hormone, or an identical placebo, was administered to 58 clinically proven cases of angina pectoris. All patients studied were determined to be euthyroid by appropriate tests (BMR, PBI, and cholesterol). Thyroid extract was administered in an initial dosage of 10 mg., 3 times daily. The dosage was increased in step-like fashion every 2 weeks until 60 mg. of thyroid extract were administered 3 times a day. In addition, an intravenous injection of 0.5 mg. of laevothyroxin was administered once each week. Vitamin B factors were given in standard dosage throughout this period.

Blood pressure, pulse and cholesterol levels, measured each week, showed no significant change. Forty-six patients maintained the same weight; 8 gained from 3 to 8 pounds; while 4 experienced significant weight loss. Although all patients have been taking maximum doses of thyroid extract for 6 to 15 months, no complications from therapy have been observed. Exercise-electrocardiographic tests have not demonstrated diminution in exercise tolerance and, in fact, have shown improved response in 6 patients. Forty-six patients reported subjective benefit as evidenced by an improved sense of well being, greater motivation, alertness and increased exercise tolerance. These observations are not only contrary to the traditional view that thyroid extract is dangerous in the presence of coronary heart disease, but also establish a rationale for its use in selected euthyroid patients with this disorder.

Hypocholesterolemic Effects of N-(1-methyl-2,3-di-p-chlorophenylpropyl)-maleamic Acid in Hyperlipemic and Normolipemic Man

Bernard A. Sachs, Ethel Danielson, and Robert Sperber, New York, N.Y.

A derivative of maleamic acid, N-(1-methyl-2,3-di-p-chlorophenyl-propyl)-maleamic acid (benz-malecene), was reported to be a potent inhibitor of cholesterol biosynthesis *in vitro* and was, therefore, studied in 3 hypercholesterolemic and 8 normocholesterolemic human subjects. Sera was analyzed for total cholesterol, α - and β -lipoprotein cholesterol, phospholipid, neutral fat, proteins and lipoproteins before, during, and after the daily administration of 1,500 to 2,000 mg. of benzmalecene for 1 to 4 weeks.

A striking drop in serum cholesterol levels, averaging 28 per cent (range 15-46 per cent), occurred promptly. In contrast to some other hypocholesterolemic agents, the fall in cholesterol appeared to be unrelated to initial control levels, i.e., per cent fall in the normocholesterolemic subjects was as great as in the hypercholesterolemic subjects. There was a profound fall in both α - and β -lipoprotein cholesterol, the former becoming immeasurable in many instances. The ratio of β : α -lipoprotein cholesterol showed marked alterations, but no trend. Associated with the fall in cholesterol was a marked but transient rise in neutral fat, which gradually returned to or below control values as the experimental period continued. The phospholipid also increased early in the experimental period in 6 of the 11 subjects.

Benzmalecene apparently interferes with the conversion of acetate and mevalonic acid to cholesterol. The rise in neutral fat is believed to be due to the diversion of available acetate from cholesterol synthesis to triglyceride synthesis. At the dose levels used, gastrointestinal complaints were prominent and interdicted prolonged study in most subjects.

Idiopathic Myocardial Hypertrophy: Report of 20 Cases

Marvin A. Sackner, David H. Lewis,† Morton J. Robinson, and Samuel Bellet, Philadelphia, Pa.

The clinical findings in 11 patients with the clinical diagnoses and 9 patients with necropsy diagnoses of idiopathic myocardial hypertrophy have been studied. The ages of these patients were 39 ± 8 years; 75 per cent were males. The patients were subdivided into 3 groups: (1) increasing intractable congestive heart failure (12

cases); (2) cardiac enlargement with minimal or no congestive heart failure (4 cases); and (3) clinical picture of portal cirrhosis (4 cases). Antecedent upper respiratory infection occurred in 35 per cent; 25 per cent of group 1 and all the cirrhotic patients had an alcoholic history. Gallop rhythm was observed in 55 per cent and functional systolic murmurs in 25 per cent of patients. The most common electrocardiographic finding were sinus rhythm, a diphasic P wave in V_1 and left ventricular hypertrophy. Chest roentgenograms showed globular markedly enlarged hearts which appeared hypodynamic to fluoroscopic examination. Cardiac catheterization carried out in 7 patients, group 1 (4 cases), group 2 (2 cases), and group 3 (1 case) revealed findings typical of those observed in congestive heart failure except in the cirrhotic patient who had normal hemodynamic findings. In none did the contour of the right ventricular pressure curve resemble that described for fibroelastosis. Ballistocardiograms and pulmonary function studies were consistent with those observed in congestive heart failure. Necropsy revealed hypertrophy and dilatation, and in most instances areas of focal interstitial fibrosis. The endocardium was thin and smooth except in area underlying mural thrombi (44 per cent of cases).

Effects of Varying Rates of Sodium Excretion upon Na^{22} Kinetics

Marvin A. Sackner, Warren D. Davidson, Herschel Sandberg, Leonard J. Fineberg, and Samuel Bellet, Philadelphia, Pa.

The present study is an assessment of the biologic decay curve of Na^{22} , the serum specific activity (per cent of injected dose Na^{22} per mEq. Na^{23}), and total exchangeable sodium (Na_E) during a prolonged observation period. Seven male subjects, aged 40 to 63 years, with no clinical evidence of abnormal fluid retention, and 2 male subjects, aged 41 and 65 years, with edema due to the nephrotic syndrome (Kimmelstiel-Wilson syndrome) and congestive heart failure (arteriosclerotic) respectively, were studied.

Twenty μc . of Na^{22} were administered intravenously and serum and 24 hours urinary Na^{22} and Na^{23} levels were determined daily for 14 to 48 days. After a control period of a week on a fairly constant sodium intake, the patients were given sodium chloride, desoxycorticosterone acetate, and diuretic agents for periods of 3 to 7 days. Daily urinary sodium excretion ranged from 20 to 579 mEq. Slopes of the biologic decay curve during control and test periods were expressed in terms

of the biologic half-life of Na^{22} ($\text{Na}^{22}_{t_{1/2}}$). The log $\text{Na}^{22}_{t_{1/2}}$ and the log Na^{23} showed a linear relationship ($r = 0.785$); the log of the 24 hour excretion ratios for the same control and test periods also showed good correlation ($r = 0.897$). The biologic half-life of the control serum specific activity was generally shorter than that obtained from the biologic decay curve by an inconstant factor. Daily serum specific activity fluctuated widely during test periods. Measurement of daily Na_E was unreliable after the initial control period. It was concluded that slopes of the biologic decay curve of Na^{22} serve as useful indices of sodium excretion.

Role of Renal Hemodynamics in Chronic Pulmonary Disease and Cor Pulmonale

Herbert A. Saltzman, Felice Manfredi,^o and Herbert O. Sicker, Durham, N.C.

The role of forward heart failure in chronic pulmonary insufficiency has not been clearly defined, although decreased renal clearances are reported after cardiac decompensation occurs. In this study, renal clearances, cardiac outputs, and pulmonary pressures were measured before and after isoproterenol infusions in 26 patients meeting clinical and laboratory diagnostic criteria for severe pulmonary emphysema.

Glomerular filtration rates (GFR) and renal plasma flows (RPF) were determined by measuring urinary clearances of infused inulin and para-aminohippurate. Cardiac catheterization was performed concurrently, permitting simultaneous measurements of cardiopulmonary pressures and cardiac outputs.

Eleven patients without past or present cardiac decompensation exhibited mean values of 3.04 L. per minute per M^2 for the cardiac index (CI), 99 ml. per minute for the GFR, 398 ml. per minute for RPF, and 26.3 for the filtration fraction. During isoproterenol infusions mean values changed to 4.55 L. per minute per M^2 for the CI, 450 ml. per minute for RPF, and to 23.4 for the filtration fraction. Seven patients, with recent congestive heart failure, averaged 2.5 L. per minute per M^2 for the CI, 85 ml. per minute for the GFR, 293 ml. per minute for RPF, and 33.5 for filtration fraction. During isoproterenol infusions, mean values changed to 4.1 L. per minute per M^2 for the CI, 332 ml. per minute for RPF and to 25 for the filtration fraction.

The results indicate that renal plasma flow can fall significantly in pulmonary insufficiency prior to the onset of overt cardiac decompensation.

The close relationship of renal plasma flow to cardiac output is emphasized by the significant rise in both functions during isoproterenol infusions. It is suggested that forward manifestations of congestive heart failure may occur early in the course of chronic lung disease.

Isometric Period of Contraction as a Determinant of Cardiac Performance and Digitalis Action

Mohinder P. Sambhi, Dallas, Tex.

Apex cardiograms, suprasternal aortograms, subclavian arteriograms, and standard limb leads were recorded simultaneously with heart sounds on 3 normal subjects and 5 patients in cardiac failure, before and after digitalization; 15 hypertensive subjects and 10 normal controls. The apex cardiogram yields a more accurate measurement of the duration of total systole than the heart sounds. Ejection period was measured from the arteriograms and the duration of the isometric phase determined. The duration of this phase ranged from 0.03 to 0.06 seconds in normal subjects, 0.07 to 0.14 seconds in hypertensive subjects, and 0.07 to 0.12 seconds following digitalization. Prolongation of the isometric phase appears to be a mechanism for compensation to work load and a response to digitalization in the failing heart. The heart rate had little effect on the duration of this phase. Its chief determinant may be the gradient of the pressure rise. On the basis of the T wave changes that the volume and work load of the heart produce in the electrocardiogram, it is postulated that length of the isometric phase governs the contraction and relaxation pattern through different effects on the inner and the outer layers of the myocardium.

Effect of Rotating Tourniquets upon Plasma Volume and Red Cell Mass

Philip Samet, William H. Bernstein, Miami Beach, Fla., and Robert J. Boucek, Miami, Fla.

Bloodless phlebotomy by means of rotating tourniquets has been a standard form of therapy in acute left ventricular failure. Acute reduction in "effective circulating blood volume" has been projected as the underlying physiologic basis for this therapy. The purpose of this study was to investigate the changes in plasma volume and red cell mass after application of rotating tourniquets by means of a newly developed automatic apparatus. Venous congestion was induced in each extremity for 30 of each 40 minute time period. Tourniquets were applied to 3 of the 4 extremities at any one time at pressures from 55-75 mm. Hg, for a 1- to 3-hour period.

Control measurements of plasma volume and red cell mass made with T-1824 and P^{32} , respectively, in 14 subjects with varied types of heart disease. After the period of tourniquet application, these determinations were repeated during the final period of venous congestion. The control average plasma volume and red cell mass totaled 2,846 and 1,636 ml. respectively. The corresponding figures after tourniquet application are 2,753 and 1,543 ml., respectively. Although slight decreases in plasma volume and red cell mass were frequently observed, a marked decrement in plasma volume was noted in only 1 patient. A pronounced fall in red cell mass occurred in 2 subjects.

The observations suggest that the clinical improvement attendant upon the use of rotating tourniquets in left heart failure is not mediated principally via a marked reduction in blood volume.

Oral I^{131} -Triolein Tolerance Curve in Patients with Diabetes Mellitus

Herschel Sandberg, Byongsok Min, Leonard Feinberg, and Samuel Bellet, Philadelphia, Pa.

Previous studies in this and other laboratories have demonstrated that patients with myocardial infarction have abnormal I^{131} -triolein tolerance curves. Because of the well known tendency for patients with diabetes mellitus to develop early atherosclerotic lesions, a study of I^{131} tolerance curves in such a population was undertaken.

A test meal containing I^{131} -triolein was administered to 28 diabetic patients ranging in ages from 19 to 75. Serial blood samples were drawn and aliquots of both whole blood and the trichloroacetic acid precipitable fraction (representing circulating lipoprotein) were analyzed for radioactivity. Fasting cholesterol, phospholipids, and triglycerides were also determined.

It was found that diabetics under the age of 60, manifesting either peripheral vascular disease or demonstrable signs of atherosclerotic heart disease, had I^{131} -triolein tolerance curves indistinguishable from those displayed by patients with myocardial infarction. The radioactivity appearing in both whole blood and circulating lipoprotein fraction reached significantly higher peak levels than in normal controls of a similar age group. This elevation persisted for 24 hours. Moreover, the fraction of the total activity present as lipoprotein in the circulating blood was markedly greater than that seen in the controls.

The diabetics under 60 years of age who had no demonstrable peripheral vascular or cardiac disease also manifested these abnormalities, but to a lesser degree. It was of interest that the I^{131} -

triolein tolerance curves of the 8 elderly diabetics ranging in age from 60 to 86, who displayed peripheral vascular and cardiac atherosclerotic lesions, were within the normal range.

Effects of Isoproterenol on Renal Function in Congestive Heart Failure

Harold Sandler, Harold T. Dodge, Seattle Wash., and Hershal V. Murdaugh, Jr., Birmingham, Ala.

This is a study of effects of isoproterenol, a drug with potent positive inotropic and chronotropic effects, on renal plasma flow (ERPF), glomerular filtration rate (GFR), urine flow, cardiac output and venous and systemic arterial pressures in 11 patients with congestive heart failure of varying etiologies without heart block. Subjects were studied during control and intravenous infusion of isoproterenol at rates of 1- γ per minute for periods up to 45 minutes. ERPF increased in all but 1 subject (increase of 18 ± 21 per cent from control of 214 ± 142 ml. per minute). Effect on GFR was slight and variable (change of 0 ± 15 per cent from control of 76 ± 31 ml. per minute). Filtration fraction decreased toward normal in all subjects from control of $.41 \pm .16$. Effect on urine flow was variable, 7 subjects increasing, 4 subjects decreasing (increase 62 ± 83 per cent from control of 2.0 ± 1.5 ml. per minute).

These changes in renal dynamics were related to the following changes in cardiovascular dynamics: in all subjects cardiac index increased (increase of 58 ± 36 per cent from control of 1.8 ± 1.2 L. per minute per M^2), while venous and mean systemic arterial pressures and systemic and renal vascular resistances decreased. ERPF increased proportionately less than cardiac output. Although renal vascular resistance decreased, the ratio of renal to systemic vascular resistance increased indicating that other vascular beds had a proportionately greater lowering of resistance.

It is of clinical interest that the acute cardiovascular-renal effects of isoproterenol are similar to those of theophylline.

Efficacy of Penicillin in Eradicating β -Hemolytic Streptococci from Tonsillar Tissue

Milton S. Saslaw, James M. Jablon, Sallie A. Jenks, and Claudette C. Branch, Miami, Fla.

Throat swabs were taken from 178 children prior to tonsillectomy. Tonsils were collected upon excision and minced. Swabs and tonsils were studied bacteriologically for presence of β -hemo

the streptococci. All organisms recovered were typed.

A second group of children (140) had throat swabs taken, but were treated with penicillin (1.2 million units of bicillin, intramuscularly, or 1.2 million units of all purpose bicillin, intramuscularly) 48-72 hours prior to tonsillectomy. Second throat cultures were taken at surgery. Tonsils were collected as above. Venous blood was drawn for antistreptolysin O titer determination.

Of the untreated cases, 56 (31.46 per cent) harbored β -hemolytic streptococci, of which 42 (23.60 per cent) were group A organisms. Among the second group of children, 30 (21.43 per cent) had β -streptococci before penicillin, of which 14 (46.67 per cent) were group A; 19 of the 30 were free of organisms after penicillin, while 11 continued to yield streptococci (3 were group A). Nine additional children in the treated group, initially negative, yielded organisms at the time of surgery. Of these 9, none were group A; 4 were group AF. Average antistreptolysin O titers on 95 of 178 untreated children were 187 Todd units (positives, 335; negatives, 112); on 122 of the 140 treated patients (2 days after treatment) titers were 173 Todd units (positives, 242; negatives, 145).

Penicillin as used in this study usually is adequate to eradicate group A β -hemolytic streptococci from tonsils. Other groups of streptococci are not as susceptible, nor are all the group A carriers affected. As a measure for prevention of streptococcal infection, penicillin probably should be employed prior to tonsillectomy, but doses larger than those utilized may be indicated.

Genetic and Environmental Influences on Circulating Lipids: Comparative Study of Two Dissimilar Populations

Louis E. Schaefer, David Adlersberg, and Arthur G. Steinberg, New York, N.Y.

An investigation of the roles of heredity and environment in determining circulating lipid levels in healthy persons was conducted in 2 separate populations in the New York City area with dissimilar environments (Staten Island and Manhattan). Both groups consisted of employed persons and their families evaluated during their annual physical examination.

The Staten Island sample consisted of 1,236 persons, of whom 755 were members of 201 families. The Manhattan sample included 1,303 persons, of whom 699 were members of 205 families.

Staten Island is semirural, Manhattan highly urban. Staten Island had 71 per cent Catholics,

Manhattan 35 per cent. Further Staten Island vs. Manhattan differences were as follows: Protestant—20 vs. 24 per cent; Jewish—9 vs. 41 per cent; White—98 vs. 86 per cent; physically-active occupations—55 vs. 8 per cent. The Staten Island population is primarily of Italian and Irish extraction, the Manhattan of Eastern and Western European origin.

The intense pace of living and/or working in Manhattan, plus a higher proportion of administrators and executives, perhaps produced a more stressful existence for the Manhattanites. The average adult Manhattan male had a higher income and 63 per cent of Manhattan wives worked full- or part-time, as compared to 23 per cent in Staten Island.

Average serum cholesterol levels related to age and sex were strikingly similar in these 2 dissimilar populations. In Staten Island, males showed constant levels to age 20, which then increased from 185 to 243 mg. per cent at age 32, and remained constant thereafter. In Manhattan, the average male level remained constant to age 20, then increased from 202 to 244 mg. per cent during the next 20 years and remained unchanged after 40.

Corresponding levels for Staten Island women were constant to age 32, then increased from 200 to 236 mg. per cent at age 58. Manhattan women's levels were constant to age 32, then increased from 201 to 280 mg. at age 58.

The slopes of curves representing change of cholesterol level with age of both sexes were almost identical in the 2 populations. In 10 of 13 five year age groups in men and in 11 of 13 in women, Manhattan values exceeded those of Staten Island by 2 to 32 mg. per cent.

Nineteen Staten Island families had a hypercholesteremic parent. Of 36 children of these families, 6 (17 per cent) were hypercholesteremic. Of 337 children of normocholesteremic parents, 8 (2 per cent) were hypercholesteremic. These children averaged 13 years of age. Twenty-five Manhattan families had a hypercholesteremic parent. Of their 43 children, 10 (23 per cent) were hypercholesteremic. Of 238 children of normocholesteremic Manhattan parents, 4 (2 per cent) were hypercholesteremic. These children averaged 18 years of age.

Correlation coefficients for serum cholesterol level among family members revealed a similar situation in both populations. The correlations between mother and father were zero. In contrast, strongly positive and statistically significant correlations existed between the levels of father-children, mother-children and sibling-sibling.

Analysis of serum phospholipid levels of the 2 populations showed age and sex trends and fami-

lial correlations similar in all respects to those of serum cholesterol.

Serum lipid levels are determined by genetic factors and modified only to a limited extent by environment influences, as exemplified by these 2 dissimilar populations.

Vascular and Connective Tissue Lesions in the Rat Associated with the Administration of Serotonin and Histamine

Arthur L. Scherbel, Roy L. McKittrick, and William A. Hawk, Cleveland, Ohio

Serotonin and histamine possess multiple pharmacologic actions and may have important functions in anaphylactoid and allergic reactions. Inasmuch as their effect on the vascular and connective tissue systems has not been clearly defined, studies were undertaken with 160 Sprague-Dawley rats injected subcutaneously with from 1 to 30 mg. of serotonin, or from 1 to 10 mg. of histamine (total dosage) for periods varying from 12 hours to 4 weeks. Morphologic alterations in connective tissue were studied by the Ivalon sponge technic. Specimens were fixed in Zenker's fluid and stained with hematoxylin-eosin-methylene blue. Mast cells were demonstrated by toluidine blue stain. Histologic sections of each animal were studied as an unknown and then compared with each other and with controls.

Significant gross and histologic alterations are summarized as follows: Serotonin increased inflammation within the sponges. Heavily granulated mast cells were seen around the sponges. Organization within the sponges was similar to that in controls. Histamine increased inflammation and hastened organization. Mast cells surrounding the sponges were scanty and degranulated. Inflammation and organization were marked when serotonin and histamine were administered simultaneously. Numerous heavily granulated mast cells were present.

Other lesions observed in rats receiving large doses of serotonin included arteritis, myocarditis, renal tubular necrosis and gastrointestinal ulceration.

It is concluded that both serotonin and histamine provoke an inflammatory reaction in rats. Histamine exerts a greater stimulating effect on organization than serotonin. An inverse relationship appeared to exist between increased organization and heavily granulated mast cells.

Relative Diuretic Activity of Chlorothiazide and Hydrochlorothiazide in Patients with Congestive Heart Failure

Mortimer L. Schwartz, Duncan E. Hutcheon, and Teruo Takasu, Jersey City, N.J.

The diuretic responses to chlorothiazide and hydrochlorothiazide were compared to those of acetazolamide and chlormerodrin in a double-blind assay using 18 patients in congestive heart failure. The drugs were each administered 3 times daily over a 1 week period alternating with 1 week intervals of placebo therapy to allow time for the edema fluid to return. Weight loss, changes in serum electrolytes, and improvement in the signs and symptoms of cardiac failure over the period of therapy were used as a measure of the diuretic response.

Equivalent diuretic effects were observed following daily oral doses of 75 mg. hydrochlorothiazide, 110 mg. chlormerodrin, 300 mg. acetazolamide and 1.0 Gm. chlorothiazide. The diuretic response to chlorothiazide and hydrochlorothiazide was accompanied by a significant decrease in serum potassium and an elevation of blood urea nitrogen. Acetazolamide caused a significant decrease in CO_2 combining power when administered at a dose of 300 mg. per day for 1 week. No toxic symptoms were noted in any of the patients receiving the aforementioned diuretics given orally at the specified levels.

Experimental Myocardial Infarction Treated with Plasmin

David W. Scott, Louisville, Ky.

In a series of dogs, thrombi were produced in the anterior descending coronary arteries at thoracotomy by the injection of thrombin (or sodium morrhuate) into an isolated segment of the anterior descending coronary artery. Treated dogs were given an infusion of a fibrinolytic preparation made from human plasma fraction III and activated with streptokinase.

The dogs were followed with electrocardiograms at intervals. They were sacrificed 3.8 days after occlusion and the volume of residual scar determined by measuring the area and thickness of scar in serial slices through the heart. The occluding thrombi, originally produced, were found at autopsy to be completely lysed in the treated group (8 dogs) and either completely occluding or virtually so in the untreated group (6 dogs). The volume of residual scar averaged 3.8 cm.³ in the 6 control animals and 0.28 cm.³ in the plasmin treated dogs.

Electrocardiographic-Pathologic Correlation Study of Left Ventricular Hypertrophy in the Presence of Left Bundle-Branch Block

Ralph C. Scott and Robert J. Norris, Cincinnati, Ohio

The electrocardiographic diagnosis of left ventricular hypertrophy (LVH) in the presence of

ft bundle-branch block (LBBB) has been considered difficult if not impossible. The present study was designed to compare the accuracy of his electrocardiographic diagnosis with the pathologic findings.

Twenty-nine cases of complete LBBB with autopsy control and without infarction were collected (13 arteriosclerotic, 14 hypertensive, 2 miscellaneous).

Electrocardiographic criteria for the diagnosis of LVH included determinations of (1) conventional criteria of high voltage; (2) index of Lewis [$(R_1 + S_3) - (R_3 + S_1)$] (3) magnitude of ΔQRS . Other electrocardiographic measurements included determination of the ventricular gradient and the direction, magnitude, and angle between the initial and terminal vectors. Pathologic criteria for cardiac hypertrophy included: (1) heart weight greater than predicted for body length; (2) left ventricular wall 13 mm. or greater; (3) right ventricular wall 5 mm. or greater.

At autopsy all 29 cases of LBBB demonstrated cardiac hypertrophy. Only 17 showed electrocardiographic evidence of LVH. At autopsy 8 of the 17 had pure LVH and 9 had combined ventricular hypertrophy. Six of the 29 cases satisfied Grant's criteria of peri-infarction block. However, no infarction or characteristic localization of fibrosis to the anterolateral wall was found. Nine cases, all with considerable hypertrophy but without anatomic infarction, exhibited Q waves (I, aV_L, V_5, V_6). Only 4 of these 9 satisfied the criteria of peri-infarction block.

Conventional electrocardiographic criteria of LVH thus occurred in only approximately 60 per cent of cases of anatomic LVH with LBBB.

Profound Hypothermia Combined with Extracorporeal Circulation for Open Heart Surgery

Will C. Sealy, W. Glenn Young, Jr., Ivan W. Brown, Jr., and Alan M. Lesage, Durham, N.C.

This report presents laboratory studies and clinical experiences with the use of profound hypothermia combined with extracorporeal circulation for open heart surgery.

In the first study, dogs were cooled to below 10 C. with an extracorporeal system and a heat exchanger and then put into complete circulatory standstill for 30 to 180 minutes. Survival rates and oxygen consumption studies indicate that 60 minutes is safe, but periods longer than this are poorly tolerated. In a second group of studies, the flow rates in the extracorporeal system were reduced as the temperature was decreased. Oxygen consumption studies show that rates of flow in the extracorporeal circulation of only 10-15 ml. per Kg. per minute are adequate for the metabolic

needs when profound hypothermia is used. In the two animal studies, 28 to 30 mg. per Kg. of quinidine was given intravenously before cooling and has been uniformly successful in preventing ventricular fibrillation. The heart went into spontaneous standstill with the temperatures used in these experiments.

The third part of this report will be a summary of the results of the use of profound hypothermia (9 to 20 C.) during the correction of a variety of intracardiac defects in man. This temperature level permits the use of very low perfusion rates; therefore only a simple pump-oxygenator was needed. Cardioplegia was induced by the cold in many of the patients. Ventricular fibrillation rarely occurred and when it did, it was easily corrected.

Electrocardiogram and Its Interpretation: Study of Opinions Given by 20 Physicians on a Set of 100 Electrocardiograms

Harold N. Segall, Montreal, Canada

The interpretation of an electrocardiogram represents the opinion of an expert and, as in other disciplines, experts sometimes differ in their opinions. How often does this happen in electrocardiography? Which records make for the maximum agreement and which for disagreement? How large is the role of the kind of training the interpreter had? How important is his total experience and the number of records he has read? Does it make any difference if he reads officially in a hospital laboratory or only in private practice? Do natural pessimists and optimists reflect their temperaments in reading electrocardiograms? And what about mood and motivation? This study attempts to answer some of these questions.

A set of 100 electrocardiograms was read by 20 experienced interpreters, who remained anonymous for the analysis of the statistical data. All 20 agreed on 21 electrocardiograms, 18 or 19 agreed on 23. A majority opinion, 14 or more interpreters, was given on 77 records, leaving 23 on which much disagreement appeared. Eight men, who do not read officially in hospitals, and the twelve official interpreters performed equally well, as measured by the number of times each man was a member of the majority or minority. Examples of maximum agreement and various degrees of disagreement have been recorded.

The rSr' in V_1 of the Electrocardiogram: Analysis of 58 Cases by Spatial Vectorcardiography

Ronald Selvester and Julian Haywood, Los Angeles, Calif.

The rSr' in right-sided precordial leads presents a difficult problem in interpretation by the conventional 12 lead electrocardiogram. This does not appear to be so when these same patients are analyzed by the timed vectorecardiogram.

Over 750 patients have been studied clinically by methods including timed vectorecardiograms, conventional electrocardiograms, and cardiac fluoroscopy in the past 2½ years at the Cardio-pulmonary Laboratory at the White Memorial Hospital. By and large, these were patients being seen in our Cardiac Advisory Conference and being considered for cardiac catheterization and cardiac surgery.

Of this total, 58 had an rSr' in V₁ with an rs ratio of less than 1, a QRS time of 0.11 seconds or less and an axis deviation of less than 110°. All but 4 of these 58 had cardiac catheterization. They included 10 patients with pulmonary stenosis and no shunt, 8 patients with mitral stenosis, 35 with left-to-right shunts (11 ventricular septal defects and 24 atrial septal defects), and 5 with no evidence of heart disease.

Of these 58, the 5 with no evidence of heart disease all had normal vectorecardiograms; 6 patients had a pattern of complete right bundle-branch block and atrial septal defects at cardiac catheterization (shortest QRS interval in this group was .08 second); 48 patients had a pattern of mild to moderate right ventricular hypertrophy. Only 1 had the vectorecardiographic pattern of incomplete right bundle-branch block.

In summary, from this data it would appear that the vectorecardiogram is definitive in separating the various causes of the rSr' in V₁ and that most of these are due to early right ventricular hypertrophy. Incomplete right bundle-branch block as a cause of an rSr' in V₁ would appear to be a rarity.

Spontaneous Intermittent Disappearance of the Typical Murmur of Patent Ductus Arteriosus

William Shapiro, Portsmouth, Va., Sami I. Said, Richmond, Va., and Phillip L. Nova, Portsmouth, Va.

A 9-year-old girl was found to have a continuous murmur which "spontaneously" disappeared for periods up to 20 minutes documented by phonocardiograms. Cardiac catheterization, while the murmur was present, revealed a left-to-right shunt at pulmonary artery level of about 3 L. per minute. Pulmonary arterial and other pressures were normal.

Attempts were made to determine whether disappearance of the murmur was associated with absence of shunt flow, and, if so, the cause of this phenomenon.

With the murmur present, physiologic dead space/tidal volume was 23 (55/238 cc.) and 30 per cent (113/375 cc.) in recumbent and upright positions, while with the murmur absent the values were 22 (37/165 cc.) and 49 per cent (137/279 cc.), respectively. In the former case, the small increase in dead space and hence less impairment of perfusion of alveoli in the upright position was consistent with the presence of an added volume of blood in the pulmonary circulation. Also, systemic arterial pulse pressure was greater when the murmur was present.

Disappearance of the murmur most consistently occurred with quietude. Posture, amyl nitrate and low and high oxygen mixtures had no effect, while anxiety made it louder.

At operation, the ductus was somewhat long and slightly kinked. Gentle dorsal traction on the pulmonary artery readily abolished the thrill. The intermittent nature of the murmur, and presumably, shunt flow was probably related to variations in cardiac output and shifts in position of some mediastinal structures. This phenomenon may render diagnosis difficult in other patients.

Simple Method for Detection of Left-to-Right Shunts

William Shapiro and Alton R. Sharpe, Jr., Portsmouth, Va.

A simple technique to detect intracardiac shunts would be useful. Precordial isotope-dilution curves yield contours similar to those obtained by dye dilution studies and were observed to change similarly in the presence of central recirculation.

Following intravenous injection of I¹³¹-albumin, a collimated scintillation counter focused over the apex and/or right ventricle inscribed curves on a direct writing linear recorder. Doses as low as 3 µc. were satisfactory, allowing serial studies in adults and consideration for use of this technique in children.

Thirty-four studies in 22 patients without shunts demonstrated rapid up- and downstrokes. Mean buildup time (B.T.) was 9.6 ± 2.7 seconds, disappearance time (D.T.) 32.4 ± 10.2 seconds, and D.T./B.T. ratio 3.7 ± 1.8 .

Twenty-two curves from 13 patients with shunts demonstrated by right heart catheterization yielded distorted downstrokes showing either higher than normal recirculation humps or gradual down-slopes. Mean B.T. was 8.9 ± 4.1 , D.T. was 63.4 ± 27.9 and D.T./B.T. 7.5 ± 2.3 . Differences in D.T. and D.T./B.T. between the 2 groups were significant ($p < 0.001$).

Three patients with bidirectional shunts did not consistently show aberrations of the upstroke. Right ventricular curves best demonstrated the abnormal downstroke in acyanotic atrial or ven-

tricular defects. Patients with patent ductus and those with small shunts had less distorted curves. Flow data gave good approximations of systemic flow, but accurate estimates of pulmonary flow were not obtained.

Precordial isotope-dilution curves offer a simple means for detecting left-to-right shunts without arterial sampling.

Arterial Thrombosis without Arteriosclerosis and the Probable Role of Increased Pulmonary Megakaryocytes in its Formation

J. George Sharnoff, Mount Vernon, N.Y.

A number of instances of coronary, cerebral and mesenteric artery thrombosis can be shown to have developed in normal arteries free of sclerosis and a possible explanation of their development is suggested. This material lends support to the contention of White that coronary artery thrombosis (or any thrombosis-author) may be produced by 2 separate factors, namely, arteriosclerosis and an as yet unknown alteration of the blood predisposing the blood to thrombosis. The concept of the second factor is no doubt derived from the all too frequent observation at the autopsy table of severe coronary arteriosclerosis without thrombosis. The observation of the above material of thrombosis without arteriosclerosis, though occurring rarely, only adds further emphasis to the possibility that the alteration of the blood alone may lead to arterial thrombosis.

It is suggested that the blood alteration which may do this is produced by the rapid addition of platelets to the blood formed from the break-up of an increased number of pulmonary megakaryocytes. It would appear from recent studies by the author in animals and humans that stress may cause an increase of megakaryocytes in the pulmonary vessels and that further stress may cause the megakaryocytes to break up rapidly into platelets under the pounding rapid heart action of the right ventricle. Associated with this platelet increase there is usually a blood hypercoagulability. The blood hypercoagulability associated with arteriosclerosis is the usual combination of factors leading to thrombosis, but blood hypercoagulability alone may also cause thrombosis.

Effects of Therapy on Lung Mechanics in Human Pulmonary Edema

John T. Sharp,[†] David G. Greene, Ivan L. Bunell, and Geraint T. Griffith, Buffalo, N.Y.*

It has been previously reported that pulmonary compliance is low and pulmonary resistance elevated in pulmonary edema in man. An attempt has been made to evaluate the acute effects of some

of the common forms of therapy upon lung mechanics in acute pulmonary edema in man. In 6 of 9 patients studied, satisfactory observations on the effect of therapy were obtained. Control (pretherapy) pulmonary compliance values were between .020 and .060 L./cm. H₂O. The types of therapy evaluated were: (1) morphine (given intravenously) in 3 instances; (2) aminophylline (given intravenously) in 3 instances; and (3) intermittent positive pressure breathing in 3 instances. Morphine had no significant acute effect on lung compliance. Aminophylline caused significant increases in lung compliance and significant decreases in pulmonary resistance in all 3 instances in which it was used. Intermittent positive pressure breathing increased lung compliance while the patient was on the breathing valve, but compliance fell quickly to or toward the pretherapy value again after cessation of positive pressure breathing.

These data suggest that at least part of the beneficial effects observed clinically with aminophylline and positive pressure breathing are due to a direct effect upon lung mechanics. Morphine probably exerts its beneficial effect in pulmonary edema by other mechanisms than a direct effect upon pulmonary mechanics.

Precordial Isotope-Dilution Curves: Analysis of the Normal Curve and Comparison with Fick Method for Cardiac Output Determination

Alton R. Sharpe, Jr., and William Shapiro, Portsmouth, Va.

Precordial isotope-dilution curves provide a simple method for determination of cardiac output without arterial sampling. Fifty-two studies in 30 males and 8 females have been analyzed.

Basal outputs were obtained, utilizing a collimated sodium iodide thallium activated crystal focused over the apex impulse or second left interspace adjacent to the sternum. The formula, *final dilution* \times *blood volume* \div *area* has been used to obtain flows. Blood volumes were obtained by the I¹³¹-albumin method corrected to approximate red cell mass as determined by the Cr⁵¹ method. Area under the primary curve was obtained by planimetry and converted to counts per minute per second.

Analysis of 34 curves from 22 normal controls revealed a rapid appearance time (range of 1 to 13 seconds and mean of 4.1 ± 2.8 seconds), rapid upstroke and an exponential fall-off, followed by initial recirculation and final equilibrium. Mean build-up time (BT) was 9.6 ± 2.7 seconds, disappearance time (DT) 32.4 ± 10.2 seconds and DT/BT ratio of 3.7 ± 1.8 .

Mean cardiac index in 24 normals was 3.77 L./min./M.² Comparison with the Fick method in 12 catheterized patients showed deviations ranging from -1 to +17 per cent in 11; +28 per cent in 1. Mean deviation was 8.7 per cent. Close duplicate values were obtained using 3 μ c. on both the first and second study on a number of occasions.

The accuracy and ease of performing this procedure make it applicable in a wide variety of clinical states.

Cardiovascular Findings in Children with Sickle Cell Anemia

Herbert Shubin, Morse J. Shapiro, Ruebin Kaufman, and David C. Levinson, Los Angeles, Calif.

Seven children with hematocrits between 18 and 27 per cent, and hemoglobin S in excess of 90 per cent showed the following cardiovascular features: (1) exertional dyspnea and fatigue; (2) systolic murmur of grade II intensity or louder, most prominent over the upper left sternal border; (3) third "filling" heart sound in 5 of the 7 cases; (4) x-ray evidence of diffuse cardiomegaly and increased pulmonary vascularity; (5) abnormal electrocardiograms in 4 cases; (6) increased blood and plasma volumes.

Right heart catheterization in these 7 patients, ranging in age from 6 to 16 years, revealed the following: (1) pulmonary artery systolic pressures below 30 mm. Hg; (2) pulmonary artery mean pressures normal in all cases at rest and with exercise; (3) low pulmonary vascular resistances; (4) normal wedged pulmonary artery pressures; (5) cardiac indices averaging twice normal; (6) increased stroke indices; (7) arterial oxygen unsaturation in all cases with arterial oxygen saturation ranging from 76 to 89 per cent while breathing room air; (8) no right to left intracardiac shunts; (9) no significant change in arterial oxygen saturations with exercise; (10) failure to achieve arterial oxygen saturation above 91 per cent even with breathing 100 per cent oxygen; (11) venous oxygen saturations ranging from 59 to 67 per cent; (12) coronary sinus oxygen saturations below 40 per cent in the two patients in whom the coronary sinus was entered.

Local Cooling of the Anoxic Heart for Elective Cardiac Arrest

Norman E. Shumway, Richard R. Lower, and Raymond C. Stofer, San Francisco, Calif.

Elective cardiac arrest is an important feature of successful open heart surgery. With the fading popularity of potassium standstill, anoxic arrest

has increased in application, but the period of safe cardiac anoxia at normal temperature is no longer than 15-20 minutes. Selective hypothermia of the heart induced by simple perfusion of the pericardial well with isotonic saline solution at 0-5 C. prolongs the duration of safe cardiac anoxia to at least 1 hour.

Twenty-one dogs were divided into 4 groups. Right ventriculotomy was performed in all. The first series of 8 dogs was submitted to 8-20 minutes of cardiac anoxia at normal temperature. Pump-oxygenator support averaged 30 minutes, longer than the period of occlusion. The remaining animals were divided into 3 groups and subjected to 30, 45, and 60 minutes respectively of cardiac anoxia with local hypothermia. The only death in any experiment came when the left atrium was not decompressed of its bronchial return. In this dog the left heart was dilated, the lung fields were flooded, and the cooling effort was less effective due to the additional mass. The period of support after aortic disocclusion with the heart-lung machine was between 30 and 50 per cent of the duration of cardiac anoxia.

Chronic "Nonspecific" Myocarditis—Forgotten Clinical Entity

Earl N. Silber, Aaron B. Shaffer, and Antonio Cahue, Chicago, Ill.

The diagnosis of chronic myocarditis, so frequent before 1900, fell into disrepute with the appreciation of the relationship of coronary artery disease to replacement fibrosis of the myocardium. During the past 10 years, evidence from clinicopathologic studies, as well as from the cardiac surgeon's table, indicates that chronic nonrheumatic myocarditis may be the "great imitator" in cardiology. Nevertheless, few physicians today ever entertain such a diagnosis when confronted by atypical or obscure instances of heart disease.

The detailed clinical, laboratory, and autopsy findings of 5 patients with chronic cardiac disability due to nonrheumatic myocarditis are presented. The features which are helpful in creating clinical awareness of this entity are pointed out. The age of the patients ranged from 26-76 years; the duration of the disease, from 1-10 years. Two of these patients masqueraded as rheumatic valvular disease; 2, as arteriosclerotic heart disease and 1 as constrictive pericarditis.

Important features in establishing the clinical diagnosis are: 1. The absence of a history of rheumatic fever in patients with heart murmurs. 2. A history of antecedent respiratory infection. 3. Unexplained cardiomegaly. 4. Apical diastolic murmurs without other confirmatory signs of mitral

enosis. 5. The presence of bundle branch system block, especially LBBB. 6. Sensitivity to relatively small amounts of digitalis.

It is important to distinguish these cases from surgically remediable heart disease and to evaluate their place in the field of chronic cardiovascular dysfunction.

Clinical Correlation of Biochemical Alterations During Major Surgery

Charles W. Silverblatt, George L. Baum, Alex M. Greenberger, Mark W. Wolcott, and Fred Wasserman, Coral Gables, Fla.

To date, no common denominator in the pathogenesis of cardiac arrest has been apparent. Hypoxia, hypercapnea, reflex changes, myocardial factors, electrolyte changes and anesthetic agents have all been incriminated.

In an attempt to determine the clinical significance of measurable biochemical alterations before, during and after surgery the following study was undertaken:

Twenty-five patients were studied prior to major surgery. During operation, arterial blood gases, pH and serum electrolytes were obtained every 30 minutes and continuous electrocardiograms and blood pressures were recorded. The patients' status was carefully noted and unusual changes were correlated with the immediate surgical manipulation. Postoperative observations were extended for 2 hours.

Of the 25 cases, 18 patients (ages 25 to 85) developed significant cardiac arrhythmias, including frequent premature atrial contractions, wandering pacemaker, nodal rhythm, first degree A-V heart block, interference dissociation and ventricular rhythms. These did not appear to correlate with age. These changes in cardiac rhythmicity closely correlated with hypotension (13 patients); hypercapnea (arterial $p\text{CO}_2 > 48$ mm. Hg) (20 patients); acidosis (arterial pH < 7.33) (17 patients); chronic debilitating illness, heart disease and chronic lung disease. All patients with compromised pulmonary function developed arrhythmias. However, normal function did not mitigate against the appearance of an ectopic rhythm. Arrhythmias were successfully treated with intravenous atropine or increased manual respiratory assistance. There have been no operative deaths.

Electrolyte changes paralleled those previously reported, except for a marked increase in inorganic phosphorus (17 cases). Fourteen of these had arterial pH's < 7.33 . The significance of the PO_4 elevation is being investigated.

Oxygen saturation < 93 per cent was observed in 17 patients at the time of induction but occurred

in only 1 during the surgical procedure itself. This was also observed during the 2 hour postoperative period (15 patients).

Influence of Lung Volume on Pulmonary Hemodynamics

Daniel H. Simmons, Leonard M. Linde, Joseph H. Miller, and Edward L. Ellman, Los Angeles, Calif.

Indirect evidence suggests that pulmonary vascular resistance (PVR) increases as the lung volume (LV) either increases or decreases from its normal resting level. Pulmonary hemodynamics were directly studied in 10 intact anesthetized dogs, ventilated with a Starling pump to maintain normal arterial pH. The pressure gradient from pulmonary artery to vein and transmural vascular pressures (against intrapleural pressure) were determined through cardiac catheters, using a differential pressure transducer. Cardiac output was determined in duplicate by the dye-dilution technique using indocyanine green. Measurements were made at normal, decreased (-33 per cent), and increased ($+75$ per cent) functional residual capacity (FRC) by changing end-expiratory pressures to -16 and $+15$ cm. H_2O with constant tidal volume and respiratory rate.

Cardiac output increased 18 per cent with the smaller FRC, and decreased 30 per cent with the larger FRC, presumably due to effects on venous return. PVR rose with both decreased and increased FRC (24 per cent and 181 per cent, respectively), indicating that LV and PVR are related by a "U-shaped curve," with minimum resistance in the region of the normal FRC. It could not be ascribed to the passive response to decreased transmural pressures in the large pulmonary vessels, since these pressures were measured directly and were found to increase in both cases. Therefore, the increase in PVR of intact animals at lung volumes, both above and below normal, appears to be due to altered geometry of the vessels, an intrinsic function of lung size.

Risk of Interrupting Long-Term Anticoagulant Treatment

Herbert S. Sise, Jacques Gauthier, and Robert Becker, Boston, Mass.

To determine the risk of interrupting long-term anticoagulant treatment, a group of 239 patients on long-term treatment predominantly for arteriosclerotic disorders was reviewed. Of 33 who stopped because of bleeding, 7 died and 4 more developed complications, all within 1 day to 3 months from the time the drug was stopped. A

common sequence of events was bleeding, admission to the hospital, transfusion, vitamin K₁, recovery from the bleeding episode, sudden unexplained death several days later, and autopsy showing myocardial infarction with or without recent thrombosis in a coronary artery. Of 30 who defaulted, follow-up studies showed 9 complications, 6 of which were fatal. A significant difference from the group who stopped because of bleeding was that all but 1 of the complications happened after 4 months. In 23 instances where anticoagulants were stopped for brief periods of 3 days to 1 month for tooth extractions or surgical procedures, there was 1 nonfatal and 2 questionable complications.

It is concluded that stopping anticoagulants for brief periods of time for tooth extractions or surgical procedures involves no great risk. On the other hand, if bleeding occurs necessitating withdrawal of anticoagulants, one may anticipate complications in the form of myocardial infarction, sudden death, or stroke in approximately 33 per cent. The reasons for this are conjectural, but under etiologic suspicions are: (1) transfusions of whole blood which may have clot promoting properties similar to, but weaker than, serum; (2) bleeding which may in some way accelerate clotting through release into the circulation of products of clotting in minute amounts; (3) vitamin K₁, which may induce an "overshoot"; and (4) stasis resulting from bed rest in the hospital. It also should be pointed out that the use of patients who have stopped anticoagulants because of bleeding, as controls to compare with those who have continued treatment, may lead to some inaccuracies.

Failure of Increased Sensitivity to Corticosterone to Account for the Development of Adrenal-Regeneration Hypertension

Floyd R. Skelton, New Orleans, La.

Failure to demonstrate increased secretion of corticosterone or aldosterone in rats with adrenal-regeneration hypertension has prompted the suggestion that transient adrenocortical insufficiency might sensitize to the hypertensive properties of these steroids. Sensitization to corticosterone as the mechanism of adrenal-regeneration hypertension was tested by administering this steroid in daily subcutaneous doses of 0.5, 1.0 and 2.0 mg. to adrenalectomized, uninephrectomized weanling female rats, given 1 per cent saline to drink starting on the day of operation and after 7 and 14 days of adrenal deficiency. Uninephrectomized, adrenal-enucleated and adrenalectomized control groups were included. Adrenal-enucleated rats were hypertensive by the end of 3 weeks when saline in-

take was also increased sharply. After 6 weeks, none of the corticosterone-treated rats had hypertension or polydipsia and at autopsy the characteristic changes of adrenal-regeneration hypertension were absent.

If adrenal insufficiency produces sensitization to renewed corticosterone secretion, the exogenous administration of this steroid to uninephrectomized salt-treated rats during the critical interval of adrenal regeneration (2 to 3 weeks) should potentiate the development of the hypertensive syndrome. This was tested by subcutaneously injecting such rats with 2.0 mg. of corticosterone per 100 Gm body weight for 5 weeks beginning on the day of enucleation and at 7, 14 and 21 days after operation. Instead of potentiation, inhibition occurred which was more marked the sooner corticosterone administration was begun after enucleation.

It is concluded from the failure of transient adrenocortical insufficiency to sensitize to the hypertensive properties of corticosterone and the inability of corticosterone administration to potentiate adrenal-regeneration hypertension that secretion of this steroid plays no significant role in the pathogenesis of the syndrome.

Implications of the Syndrome of Acute Idiopathic Pericarditis

Alfred Soffer, Rochester, N.Y.

Twenty-seven cases of acute "benign" idiopathic pericarditis were observed for periods of from 1 to 10 years. These patients (18 men and 9 women, with an average age of 38) experienced marked gradations of clinical severity and frequency of pain, leukocytosis, fever, friction rub, cardiomegaly, pulmonary involvement, recurrences, response to triamcinolone, arrhythmias, and shock.

It is concluded that: 1. New insight as to the etiology of idiopathic pericarditis is provided by its resemblance to viral myocarditis, postsurgical polyserositis, and allergic pericarditis. The post-myocardial infarction syndrome is also strikingly similar to idiopathic pericarditis, and anticoagulants are contraindicated in both diseases. 2. Present understanding makes it possible to remove Coxsackie virus pericarditis from the "idiopathic" category. Steroid therapy may be dangerous in these cases. 3. Contrary to accepted concepts, the electrical systole corrected for rate (QTc) was consistently normal in all 3 phases of electrocardiographic evolution. 4. Review of 415 cases of acute idiopathic pericarditis, reported by 36 authors, revealed that 222 patients had follow-up observations and, in 12 instances, persistent electrocardiographic abnormalities were present. In this series, 3 young men (ages 20, 28, and 30) evidenced coro-

nary T waves or changing injury currents for from 1 to 10 years, and in 2 cases, the abnormalities appeared in the absence of significant cardiovascular symptoms. This illustrates the author's thesis that idiopathic pericarditis may be present with a striking paucity of characteristic stigmata.

Electrocardiographic Effects of Injecting Potassium and other Ions into a Coronary Artery of the Intact Dog

Louis A. Soloff, Guido Ascanio, and Morton J. Oppenheimer, Philadelphia, Pa.

The electrocardiographic changes of acute myocardial infarction may be related to regional chemical changes within the myocardium. West's technique of catheterizing a coronary artery was utilized to produce a variety of regional chemical changes within the otherwise healthy myocardium of the intact dog. This report is concerned with the electrocardiographic effects of potassium and other ions so used.

As little as 20-60 mg. KCl in a 10 Kg. dog immediately reverses the polarity of the T wave. Within a few seconds, a diastolic injury current appears. This current is characterized by a depression of the diastolic base line and elevation of S-T takeoff. As this injury current increases over the next few seconds, T slowly returns to its original direction, but with increased magnitude. As this injury current decreases over the next few seconds, the S-T segment becomes cove-shaped and the T wave again reverses its polarity. This pattern persists for a few seconds and then gradually returns to the pre-injection contour. With larger doses of potassium, the injury current is preceded by 1 or several premature beats. With still larger doses, ventricular tachycardia may follow the appearance of the injury current. At this time, necropsy sometimes discloses a small myocardial infarction. These electrocardiographic changes are reversible. With larger doses, irreversible ventricular fibrillation at a ventricular rate of about 1,200 per minute develops. The only consistent electrocardiographic depressant action of potassium in this sequence of events is (with larger doses) an early brief minimal slowing of sinus discharge. Potassium on occasion can, however, give results indistinguishable from acetylcholine when injected by the intracoronary route so as to reach selectively the A-V node. This reaction is characterized by transient complete ventricular standstill with sinoauricular action undisturbed.

Lithium chloride, CaCl_2 , MgSO_4 , NaOH and HCl require at least 200 times the minimal effective dose of KCl to produce electrocardio-

graphic changes. Only lithium chloride produced sequential changes comparable to those of KCl. However, in this case, the initial change in the polarity of the T was gradual rather than the abrupt one seen with KCl. Animal Ringer's solution produces no electrocardiographic changes. Sometimes, 0.9 per cent NaCl and CO_2 gas may produce a change in the voltage of the T wave when injected slowly into otherwise normal hearts.

Ions injected into a coronary artery of the intact dog produced sequential electrocardiographic changes different from those seen when the total heart is exposed to these ions. Of all substances tested, the electrocardiogram was most sensitive to potassium. The sequence of changes produced by potassium could not be duplicated by other ions. Potassium so injected, depending upon the dose, brought about reversible or irreversible myocardial infarction.

Cine-Coronary Arteriography

F. Mason Sones, Jr., Earl K. Shirey, William L. Proudfit, and Richard N. Westcott, Cleveland, Ohio

A safe and dependable method has been devised for contrast visualization of the coronary arteries to objectively demonstrate atherosclerotic lesions.

The ascending aorta is catheterized by an approach from the right brachial artery, in the antecubital fossa. Selective opacification of the right and left coronary arteries is performed serially by injecting 20 to 30 ml. of 90 per cent Hypaque into the right and left sinuses of Valsalva adjacent to the orifices of the vessels during x-ray motion picture photography of the area of distribution of each vessel. Adequate opacification has been obtained without resorting to mechanical aortic occlusion or cardiac arrest with acetylcholine.

In more than 50 patients studied by this technique, a broad spectrum of problems has been encountered, ranging from iatrogenic disease to multiple total occlusions in those with remote and recent myocardial infarction. Selective coronary artery opacification has not produced angina, ventricular arrhythmias, or myocardial injury, even in patients experiencing angina at rest.

The method has demonstrated: 1. The presence of normal coronary arteries in patients with chest pain or electrocardiographic changes which had been interpreted as indicating the presence of arteriosclerotic heart disease. 2. Complete or partial segmental occlusion of 1 or more major arteries. 3. The presence of collateral arterial channels from 1 major artery to the area of distribution of another totally occluded segment.

The ultimate usefulness of the method remains to be defined, but it should provide a more objective diagnostic standard than has previously been available for the evaluation of therapeutic measures which have been or may be applied in the treatment of arteriosclerotic heart disease.

Does Blood Pressure Normally Increase with Age?—Thirty Year Follow-Up Data on the Labor Force of a Chicago Utility Company

Jeremiah Stamler, Howard A. Lindberg, David M. Berkson, and Wilda A. Miller, Chicago, Ill.

A statistical analysis of serial blood pressure and weight data was made over a 30 year period, from young adulthood to middle-age, on several hundred men in the labor force of a Chicago utility company. An average of 11 blood pressures per person were available for this epidemiologic study.

For the group as a whole, a moderate increase occurred in mean blood pressure with age. However, a significant per cent with low normal pressures as young adults maintained these without any significant rise throughout middle age. Such persons had markedly lesser risk of developing coronary heart disease and other cardiovascular-renal diseases in middle age than men exhibiting a rise in blood pressure over the decades. It would appear that a rise in blood pressure is not an invariable concomitant of aging, and cannot be indiscriminately viewed as a normal phenomenon.

Histories of Over 200 Persons, Originally Healthy, Followed until Death or for 20 Years after Their First Ballistocardiograms

Isaac Starr and Francis C. Wood, Philadelphia, Pa.

Ballistocardiograms were first taken in 1936 and within the next few years many healthy persons were tested to provide normal standards. Over 200 of these have been followed up. Thirty-two are dead, 34 others have become ill and have entered a hospital. Eighty have returned for a follow-up study, 60 have replied to a questionnaire, and 23 others are well known to us. The men and women have been arranged in order of the amplitude of their original ballistocardiograms. The 174 males can be divided arbitrarily into 2 groups. In that with the larger ballistocardiograms, 3 per cent of 117 subjects developed undoubted heart disease, and an additional 3 per cent a doubtful cardiac status. Of the 57 with smaller ballistocardiograms, 51 per cent developed undoubted heart disease and 14 per cent a doubtful cardiac status. These are highly sig-

nificant differences. The data secured on women are confirmatory, but not so striking. In this series, unselected, as far as we can determine, persons with small ballistocardiograms showed a dramatically higher death rate in the next 20 years than those with larger complexes and a much higher incidence of, and death rate from, heart disease.

Safe and Practical Method of Intravenous Abdominal Aortography, Peripheral Arteriography and Cerebral Angiography

Israel Steinberg, Nathaniel Finby, and John A. Evans, New York, N.Y.

The Robb-Steinberg method of intravenous angiocardiography by the rapid injection of concentrated organic iodides and precisely timed roentgenography has been standard for over 20 years. Utilizing the same principles, and with rapid, simultaneous, intravenous injections into both arms, the abdominal aorta, peripheral arterial and cerebral circulations (almost total angiography of the circulatory system) is achieved.

The patient lies supine on an x-ray table that contains a Bucky grid and the special 12 gage needle-stopcock units are then inserted percutaneously or by cut-down. A circulation time via this needle with 3 ml. sodium dehydrochlorate and 15 cc. saline solution is obtained. A 2 second roentgen exposure of the abdomen is made $\frac{1}{2}$ second after the bitter taste. For peripheral arteriography, a portable apparatus exposes the legs immediately after the abdominal study. For cerebral angiography, serial films at 1 second intervals are secured, beginning 2 seconds before the systemic circulation time for a total of 10 seconds.

Forty-one patients have had only mild and transient heat after equally divided intravenous injections of a highly concentrated mixture of sodium and methylglucamine diatrizoates (average dose, 1 ml. per Kg.). The abdominal aorta and peripheral arteries were well visualized in all but 1 instance. In 6 patients, a second injection was needed for more complete opacification. Only 4 patients had studies of the cerebral circulation. Among the noteworthy findings were arteriosclerotic abdominal aortic and splenic artery aneurysms, a ruptured spleen, a postlaminectomy aorticoinferior vena cava fistula, and arteriosclerotic abdominal aortic and peripheral endarteritis.

Reduction of Serum Cholesterol Level in Patients with Coronary Atherosclerosis by Oral Neomycin

Alfred Steiner, Martin Finkel, and Jenos Bakke, New York, N.Y.

A previous report has demonstrated that the oral administration of neomycin to 10 patients with coronary atherosclerosis resulted in a consistent fall in the level of serum cholesterol. These studies have been extended. Daily oral administration of neomycin (0.5 to 4 Gm.) to 22 patients resulted in an average decrease of 20 per cent in the level of serum cholesterol. The fall occurred within 2 weeks and was maintained for 1 to 5 months, the duration of the drug administration. No significant side effects were observed. The total serum lipids and the serum phospholipids also decreased. The serum cholesterol-phospholipid ratio remained unchanged.

In a study of the effect of other antibiotics, penicillin, streptomycin, bacitracin, chloromycetin, tetracycline, and kanamycin, on the serum lipids, only kanamycin was found to produce a hypocholesterolemia. Its action was not as pronounced as that of neomycin.

Studies concerned with the possible mechanism of action of neomycin in depressing the serum cholesterol level were carried out. These included fat absorption studies and experiments designed to clarify the significance of the alteration of the intestinal flora as the mode of action of neomycin.

P Wave External Cardiac Stimulator

Sam E. Stephenson, Jr., Philip C. Jolly, and L. H. Montgomery, Nashville, Tenn.

The increasing interest in temporary and permanent heart block has prompted us to seek a more physiologic approach to extracardiac pacemaking. A unit has been developed which detects the auricular P wave and uses the amplified P wave to trigger a variable ventricular stimulator. The study encompasses approximately 35 dogs whose normal cardiac rhythm has been disrupted. Determination of the electrocardiogram, electroencephalogram, venous pressure, arterial pressure and pulse and cardiac output have been made. The P wave cardiac pacemaker quickly returns to normal the elevated venous pressure, decreased arterial pressure, peripheral pulse and cardiac output. Similar normality can be obtained with timed external pacemakers slowly and then only by trial and error. Long-term observation on the experimental animals subjected to complete heart block revealed marked hemodynamic changes and late manifestations of marked ascites.

Outflow Tract Patch

Aaron M. Stern, Norman S. Talner, Delbert E. Toblitt, and Herbert E. Sloan, Jr., Ann Arbor, Mich.

Direct ventriculoplasty, with the insertion of an Ivalon patch for the relief of infundibular stenosis in tetralogy of Fallot, has resulted in the absence of cyanosis and the ability to exercise on almost equal terms with normal children. In our experience, however, this functional improvement has been accompanied by an undesirable increase in size and alteration of the cardiac silhouette.

Seven patients with tetralogy of Fallot were studied with angiocardigraphy, before and from 3 to 18 months after an Ivalon gusset had been inserted into the right ventricular outflow tract. In addition to the loss of cyanosis and digital clubbing, these children had a heave, a coarse thrill, and a harsh systolic murmur in the third interspace to the left of the sternum. Five children also had a diastolic murmur in this location. All of the postoperative chest films revealed an increased convexity of the outflow region of the right ventricle. By means of the contrast studies, this bulge was shown to be a dilatation at the patch site. In each instance, it was noncontractile. In comparing the interval chest x-rays, it would appear that the patch site enlarges with time.

Coagulant Properties of Normal and Arteriosclerotic Blood Vessels

Thomas D. Stevenson and George R. Schrodt, Louisville, Ky.

Recent studies have shown that the thromboplastic property of blood platelets is due to their phospholipid content. Since atheromas are composed in part of phospholipid, studies have been performed to determine if this material has coagulant activity. Saline suspensions of the intima, media and isolated plaques of arteriosclerotic aortas have been utilized as a source of thromboplastin in the 1 stage prothrombin time determination and prothrombin consumption test, and substituted for platelets in the thromboplastin generation test. The suspensions prepared from arteriosclerotic vessels have been compared with suspensions prepared from the intima and media of normal blood vessels and with a saline suspension of brain.

As demonstrated by these techniques, the suspensions prepared from arteriosclerotic vessels possess definite thromboplastic activity. The arteriosclerotic plaques are the most potent source of thromboplastic activity and the normal vessels possess only slight activity. The substance in the suspensions responsible for thromboplastic activity has not been isolated. It is soluble in acetone and ether and inactivated by heating.

The factors which precipitate thrombosis in arteriosclerotic vessels have not been clearly identified. The presence in the atheroma of material capable of initiating coagulation suggests that biochemical factors may be as important as rupture of plaques or intimal hemorrhage in precipitating thrombosis.

The coagulant properties intrinsic to the atheroma, as demonstrated in this study, may be of prime importance in initiating thrombosis in arteriosclerotic vessels with decreased blood flow. The demonstration of this activity in arteriosclerotic vessels provides a sound basis for prolonged anticoagulant therapy in subjects with arteriosclerotic vascular disease.

Streptococcal Infections in Adolescents and Adults after Prolonged Freedom from Rheumatic Fever

Gene H. Stollerman, Eloise E. Johnson, and Burton J. Grossman, Chicago, Ill.

Chemoprophylaxis was discontinued in a group of 285 adolescents and adults who had been followed for at least 5 years after their last attack of rheumatic fever, and the incidence and complications of streptococcal infections were subsequently determined by serial throat cultures and serum antibody determinations at least bi-monthly.

Ninety-two streptococcal infections occurred during 439 patient years and were classified as follows: (1) clinical (symptomatic), 16; (2) subclinical, proven by antibody response, 51; (3) "questionable," manifested by positive throat cultures without antibody response, 25. Only clinical infections were treated with antibiotics.

The streptococcal infection rates were as follows: (1) in adolescents (11-22 years), 24 per cent per patient year; and (2) in adults (23-70 years), 13.6 per cent per patient year. There were 3 rheumatic recurrences in the adolescents; none in adults.

The data were compared with those of children 5-15 years of age receiving prophylaxis in concomitant studies at Children's Memorial Hospital in Chicago and at Irvington House in New York. Comparison of recurrence rates was as follows: 1. Per cent recurrences per patients year were (a) patients off prophylaxis: adults, 0; adolescents, 1; (b) patients on prophylaxis: Chicago children, 2.4; New York children, 2.1. 2. Per cent recurrences per streptococcal infection (a) patients off prophylaxis: adults, 0; adolescents, 4.1; (b) patients on prophylaxis: Chicago children, 14.9; New York children, 13.4.

There was, therefore, a downward trend with age, not only in streptococcal infections but in

the frequency with which these infections reactivated rheumatic fever.

Effects of Limited Periods of Zero Gravity on the Cardiovascular System

Leonard J. Stutman and Robert N. Olson, Dayton, Ohio

The purpose of this investigation was to study the effects that entry into a zero gravity field and re-entry into the positive gravity field will have on the cardiovascular system. A twin engine C-131B was used to fly double Keplerian parabolas to give two 15 second periods of zero gravity. A tilt table, to change the attitude of the subject's body, was placed in the rear of the aircraft along with suitable recording devices for measuring simultaneous electrocardiographic lead, blood pressure, pulse rate, and plethysmographic changes in the extremities.

Three subjects without any history of cardiovascular disease were placed at 0°, 45°, 90° and rotated from 0° to 45° to 90° while in the zero gravity field. There was no change in the electrical axis of the heart on entry into the zero gravity field, during the zero field, or on re-entry into the positive gravity phase. Significantly, the pulse rate during zero gravity was markedly slowed and speeded up to its normal rate during the return to positive gravity. No change in the P-R, QRS, Q-T intervals or amplitude was noted. Blood pressure during the zero gravity period dropped 10-20 mm. Hg systolic/diastolic. Of marked interest was the varying degree of peripheral blood pooling noted in the zero gravity phase. This has implications concerning the necessity for a mechanism for passive muscular exercise during long periods of zero gravity.

While these data were collected during short periods, predictions can nevertheless be made as to the type of equipment necessary to sustain a formerly earth-bound man in space.

Effect of Magnesium on the Electrocardiogram, Action Potential and Contractility of the Mammalian Ventricle

Borys Surawicz, Eugene Lepeschkin, and Herman C. Herrlich, Burlington, Vt.

Isolated rabbit hearts were perfused with Krebs-Henseleit solution containing varying calcium-magnesium ratios. Ventricular monophasic action potentials were recorded with flexible suction electrodes simultaneously with electrocardiograms and left intraventricular pressures. When the solution contained 1.25 mEq. per L. Ca^{++} $\frac{1}{4}$ of "normal") or less, the duration of the plateau of

The action potential was determined by the concentration of Mg^{++} in solution: With "normal" Mg^{++} concentration (2.4 mEq. per L.) the plateau lengthened progressively for 30-60 seconds, and then gradually shortened. With Mg^{++} concentrations of 9.6, 19.2, or 38.4 mEq. per L., the plateau lengthened less while the subsequent shortening was more pronounced. This effect was most marked with highest Mg^{++} concentration. With Mg^{++} concentration of 1.2 mEq. per L., secondary shortening of the plateau did not occur. With Mg^{++} concentration of 0.6 mEq. per L. or less, the plateau underwent progressive lengthening, and occupied nearly the entire cardiac cycle. The duration of S-T always paralleled the plateau duration. When the solution contained 5.0-20.0 mEq. per L. Ca^{++} , high and low Mg^{++} concentrations had no appreciable effect on the duration and shape of the action potential. Intraventricular pressures were not affected by changes in Mg^{++} concentration at any Ca^{++} concentration. The following interpretations were made: 1. In calcium deficiency, magnesium appears to substitute for calcium in its effect on action potential but not on force of contraction. 2. Abnormally high or low magnesium concentrations affect ventricular repolarization when calcium concentration is decreased but not when it is normal or increased.

Congenital Mitral Insufficiency

Norman S. Talner, Aaron M. Stern, and Herbert E. Sloan, Jr., Ann Arbor, Mich.

Congenital mitral insufficiency may result from endocardial fibroelastosis, anomalous insertion of the chordae tendineae, duplication of the mitral orifice, and mitral valve clefts. In addition, "mitral incompetence" may be associated with corrected transposition of the great vessels. Although congenital mitral incompetence is apparently rare, in itself it may be so severe as to necessitate surgical intervention.

Seven patients with this lesion, varying in age from 9 months to 6 years, were evaluated at the University of Michigan Medical Center. The salient clinical features include growth retardation and the development of congestive heart failure. Each patient had a pansystolic regurgitant murmur which was localized to the apex and transmitted toward the left axilla. The electrocardiograms were not distinctive, although left axis deviation and left ventricular hypertrophy predominated. The roentgenographic examinations revealed evidence of enlargement of the left atrium. In 3 instances, this chamber was aneurysmally dilated. Angiocardiology demonstrated enlargement and large

volume changes of the left atrium and ventricle. Cardiac catheterization revealed minimal to moderate elevation of the pulmonary artery pressures. Wedge pressures, when obtainable, were also elevated. Left atrial pressure pulses obtained at the time of surgery were typical of mitral insufficiency.

Surgical correction utilizing extracorporeal circulation has been carried out in 3 instances with objective improvement. It is hoped that the gratifying results from mitral valvuloplasty in these patients will stimulate a search for others with this condition.

Relative Inotropic Actions of Some Steroids upon Isolated Cardiac Tissue

Ralph D. Tanz, Memphis, Tenn.

In an attempt to correlate chemical structure with cardiac activity, most of the previous workers have investigated the significance of either the sugar or lactone portions of the cardiac glycosides. Certain steroids were tested for their direct inotropic activity, primarily through the use of the cat papillary muscle preparation, with certain modifications developed in the course of this work. The results presented for each steroid were obtained in 7-10 separate experiments, each experiment having a duration of 3 hours. The addition of several glucocorticosteroids, cortisone (1 μ g. per ml.), and prednisone (20 μ g. per ml.), resulted in a very slight positive inotropic action in comparison to the controls.

However, when mineralocorticosteroids were added, DOCA (0.5 μ g. per ml.) and 9- α fluorohydrocortisone (1 μ g. per ml.), an immediate and very marked positive inotropic action resulted, having a duration of less than 1 hour. Ouabain (0.02 μ g. per ml.) also resulted in a marked positive inotropic action but remained elevated throughout the 3 hour experimental period. The addition of an adrenocortical-like steroid possessing a C^{17} lactone, Spirolactone (1 μ g. per ml.), resulted in a biphasic curve characterized by an initial positive inotropic action, and secondarily, a more prolonged and elevated duration. Qualitatively, this was also true for the water soluble steroid, 14- α hydroxy-S-21-succinate (2 μ g. per ml.). On the basis of these results it would appear that: (1) positive inotropic effects result from mineralocorticosteroids acting directly upon cardiac tissue; (2) the degree of this action may be related to a substance's mineralocorticosteroid potency; and (3) the presence of a lactone, although it undoubtedly manifests a direct action itself, may be responsible for the persistency of action.

Rheumatic Fever in Monozygotic and Dizygotic Twins

Angelo Taranta, Seta Torosdag, Irvington, N.Y., Julius D. Metrakos, Wanda Jegier, Montreal, Canada, and Irene Uchida, Toronto, Canada*

The tendency of rheumatic fever to "run in families" has long been known, but its relation to genetic or environmental factors is still unsettled. This problem can be studied in: (1) subjects with similar genes in the same and in different environments; (2) subjects in the same environment with identical or different genes. A situation approaching (2) is provided by twins, who constitute the object of this study.

Fifty-six index cases, who fulfilled the Jones diagnostic criteria for rheumatic fever, and their respective co-twins, were medically examined and the zygosity determined. Sixteen pairs were diagnosed as monozygotic on the basis of identical blood groups, similarity of dermatoglyphics and hair and eye color, etc. Of these 16 pairs, 3 were concordant for rheumatic fever and the kind of rheumatic manifestation was also concordant. Twenty-three pairs of the same sex were dizygotic because of differences in 1 or more blood group systems and/or marked differences in dermatoglyphics. One of these 23 sets was concordant for rheumatic fever and for its manifestations. The remaining seventeen pairs were dizygotic because they were of different sex. One of these pairs was concordant for rheumatic fever, but the clinical manifestations were different.

These data are consistent with, but do not prove, the hypothesis that genetic factors play a role in the etiology of rheumatic fever. They indicate that these hypothesized factors have only limited penetrance, since less than one fifth of the monozygotic twins were concordant for rheumatic fever.

**Corrective Surgery vs. Blalock-Taussig Operation:
Based on 10 Year Follow-Up on Patients with Blalock-Taussig Operation**

Helen B. Taussig, H. Crawford, S. Z. Palaganio, and S. Zaccarodiacus, Baltimore, Md.

This report concerns a 10 year follow-up on 224 patients who were living 5 years after a successful Blalock-Taussig anastomosis: 44 per cent of this group are doing well; 42 per cent have failed to maintain their improvement; 14 per cent have died.

An analysis of the 53 patients who have had a second operation shows that in only 10 was this required within the first 5 years; the remaining 43 required operation during the next 5 years.

Analysis of the age of these patients at first operation shows that only 2 of the 42 patients operated on between the ages of 8 and 12 have required a second operation within 10 years whereas of the 133 patients operated on between the ages of 2 and 8, 33 (or approximately ¼) have required a second operation, but only 7 per cent within 6 years.

Young children clearly do less well than older children because of the severity of the condition and because of the small size of the heart and great vessels. In some instances, the anastomosis failed to grow and in others the stenosis became more severe. Growth, however, is also an important consideration for children who have total correction. If the stenosis is not completely relieved, it tends to increase with growth. If a patch is necessary, there is no hope that the patch will grow. Although total correction is the ideal, the authors believe that an anastomosis is better for infants and small children, and corrective surgery, if necessary, after they have attained their growth.

Instantaneous Left Ventricle Dynamics During Normal Sinus Rhythm and During Ventricular Ectopic Beats

Gerald E. Thomson and Edward W. Hawthorne, Washington, D.C.

Recordings were made simultaneously in 15 open chest dogs of instantaneous changes in left ventricular cross sectional area, length index, central aortic and left ventricular pressures, and lead II of the electrocardiogram. Instantaneous changes in left ventricular cross sectional area, at the base, middle, and apex were recorded, either separately or simultaneously, by the use of the principles of electromagnetic plethysmography. The index of left ventricular length was obtained by using a strain gage caliper fashioned of shim metal, and a Baldwin SR4 strain gage. This caliper was attached along the vertical axis of the left ventricle and incorporated in an appropriate bridge circuit. Ectopic ventricular beats were produced either by epinephrine, digoxin, or direct left ventricular stimulation. The characteristic pattern of dimensional changes recorded from the left ventricle during normal cycles featured initial shortening with increase in cross sectional area of the left ventricle during the period of "isometric contraction" (asynchronous contraction). During the phase of ejection the major dimensional change was a decrease in cross sectional area. In ventricular ectopic beats, where ejection was not accomplished, the sole dimensional changes were those of a decrease in ven-

ricular length accompanied by increases in cross sectional area. These observations suggest that the increase in left intraventricular pressure occurring prior to ejection is due mainly to a decrease in length of the chamber, whereas ejection is the resultant of sustained shortening and a sudden decrease in cross sectional area.

Treatment of Heart Block with Chlorothiazide

Louis Tobian, Minneapolis, Minn.

It has been shown previously that the heart block associated with hyperkalemia can be relieved by lowering serum potassium to normal. It therefore seemed possible that heart block in patients with normal serum potassium could be relieved by mild depletion of body potassium. Two patients with frequent Stokes-Adams attacks for several months were completely freed of attacks on 500 mg. of chlorothiazide plus 6 Gm. of NaCl daily. When the chlorothiazide and salt were discontinued, attacks recurred in both patients. When the medication was again given, the attacks again disappeared completely. Balance studies indicated that potassium depletion existed in both patients while they were on the drug, even though the serum potassium was normal. The arterial pH was 7.5 in both patients, an indication of the usual mild alkalosis of potassium deficiency. The drug showed no side effects. In all likelihood, both potassium depletion in the A-V node and Purkinje fibers and the mild alkalosis contributed to improving cardiac conduction. The mild alkalosis would potentiate adrenergic influences and inhibit cholinergic influences on cardiac conduction.

Electrocardiographic Alterations Following Incision of the Right Ventricular Conduction System

Herman N. Uhley and Laurence M. Rivkin, San Francisco, Calif.

A frequent aftermath of intracardiac surgery has been the development of electrocardiographic conduction defects. In order to explain these changes, experiments were performed in dogs wherein incisions were variously made in the mural and septal walls of the right ventricle, and the induced electrocardiographic changes were correlated with the anatomic distribution of the right ventricular conduction system.

Thirty dogs were placed on total cardiac bypass using a bubble oxygenator. Through a small incision in the right ventricle, a single specific area of the septum was sharply incised in each dog. Electrocardiograms and vectorcardiograms were recorded serially throughout each experiment.

Following sacrifice, the conduction system was delineated by the application of Lugol's solution, which readily permitted the accurate localization of the lesions in relation to the conduction system. Lesions in the main right bundle resulted in classical patterns of right bundle-branch block with terminal prolongation of QRS complexes. In sharp contrast, lesions of the primary peripheral branches did not induce QRS prolongation, but resulted in changes in the S waves (terminal forces). Consistent but different patterns occurred, depending on which of the 3 primary peripheral branches of the right bundle were involved.

It was possible to predict electrocardiographic changes following specific incisions in the canine right ventricular conduction system. Results demonstrate the usefulness of above methods for clarification of the electrocardiographic pattern due to central and peripheral conduction defects, and the findings may have additional clinical application because of similarities of canine and human conduction systems.

Syndrome of Traumatic Mitral Regurgitation Following Mitral Commissurotomy

Joseph F. Uricchio, Albert N. Brest, William Likoff, and Harry Goldberg, Philadelphia, Pa.

A frequent but often unrecognized complication of mitral commissurotomy is the appearance of mitral regurgitation. In a careful review of 1,021 patients with pure mitral stenosis proven at surgery, 380 (37 per cent) cases were considered postoperatively to have varying degrees of mitral incompetence. Fifty-eight (5.6 per cent) were classified as dynamic by the surgeon because of a tear into the leaflet substance or by the severance of supporting chordae tendineae.

A classification of traumatic mitral regurgitation is presented and the clinical course of these patients is described over a follow-up period extending up to 9 years after cardiac surgery. Class I (79 per cent) consists of patients with sustained clinical improvement following mitral commissurotomy despite the presence of some mitral incompetence. Class II (9 per cent) represents those with only temporary clinical improvement while class III (3 per cent) represents those who deteriorate immediately after commissurotomy. Class IV (9 per cent) are those who fail to survive commissurotomy because of the creation of lethal regurgitation.

The cardiac auscultatory, roentgenographic, and electrocardiographic features of this syndrome are helpful in diagnosis but in the equivocal case cardiac ventriculography must be performed. Diagnosis is important because of the availability

of open surgical methods for correcting the traumatic mitral regurgitation. Recognition of this syndrome may explain the failure of some patients to benefit from mitral commissurotomy.

Clinical and Hemodynamic Features in Advanced Rheumatic Mitral Regurgitation

Joseph F. Uricchio, Lamberto G. Bentivoglio, Harry Goldberg, and William Likoff, Philadelphia, Pa.

Sixty-five patients with surgically proven pure rheumatic mitral regurgitation constituted the material for this report. Sixty-six per cent were females. The ages ranged between 13 and 54 years with an average of 33. A history of rheumatic fever was obtained in 80 per cent. Recurrent attacks were noted in 37 per cent.

The asymptomatic interval ranged from the immediate post rheumatic fever period to 34 years, averaging 10.6 years. Dyspnea then developed in 91 per cent, fatigue in 90 per cent, orthopnea in 46 per cent, nocturnal dyspnea in 33 per cent and hemoptysis in 18 per cent. Seven per cent had at least 1 embolization. Right heart failure occurred in slightly less than 25 per cent. Fifty-seven pregnancies in 27 patients were responsible for 6 bouts of pulmonary edema. Eighty-two per cent were grouped in class III or IV of the American Heart Association.

An apical pansystolic regurgitant murmur, grade 3 or louder, was noted in 78 per cent, while a midlate diastolic rumble was present in 62 per cent. Protodiastolic gallop rhythms were common. Atrial fibrillation was present in 75 per cent.

A review of the electrocardiograms revealed a normal ventricular complex in 50 per cent, left ventricular hypertrophy in 30 per cent, combined ventricular hypertrophy in 5 per cent, and right ventricular hypertrophy in 15 per cent. On x-ray, significant enlargement of the heart was present in 90 per cent.

The cardiac output ranged from 1.9 to 5.9 L. per minute with an average of 3.2 L. per minute. Cardiac index averaged 2.0 L. per minute per M.² The total pulmonary resistance ranged from 196 to 1,940 dynes sec. cm.⁻⁵ with a mean of 810. Pulmonary hypertension was present in 83 per cent. Left atrial mean pressure was increased in 90 per cent and averaged 17.4 mm. Hg. Fifty per cent of those studied by left heart catheterization had a ventricular filling gradient of mild degree especially during early diastolic. Left ventricular end-diastolic pressures were at the upper limits of normal.

Relationship of Hepatic Blood Flow and Oxygen Consumption to Total Systemic Perfusion Rate During Cardiopulmonary Bypass

John A. Waldhausen, Carlos R. Lombardi, James A. McFarland, William P. Cornell, and Andrew G. Morrow, Bethesda, Md.

Transient alterations in tests of liver function have been observed in some patients following operations with cardiopulmonary bypass. To determine if these changes resulted from inadequate liver blood flow or oxygenation, these parameters were measured in normal dogs at various rates of systemic flow.

Complete cardiopulmonary bypass was instituted utilizing a rotating disc oxygenator. The total systemic flow (perfusion rate) was recorded with an electromagnetic flowmeter, and hepatic artery flow was determined with a rotameter. Hepatic venous flow was collected at timed intervals from an isolated segment of the inferior vena cava. The oxygen content of hepatic arterial and venous blood and portal venous blood was determined by spectrophotometric or manometric analysis.

The total hepatic blood flow and oxygen consumption averaged 33.4 ml. per minute per kg. body weight and 5.8 ml. per 100 Gm. liver per minute respectively, at a flow rate of 2.8 ± 0.1 L. per minute per M.² Hepatic blood flow and oxygen consumption remained within the normal range until the systemic flow was reduced to levels between 2.2 and 1.8 ± 0.1 L. per minute per M.² At a systemic flow of 1.0 ± 0.1 L. per minute per M.², the total hepatic flow was reduced by 39 per cent while the hepatic oxygen consumption was reduced by 60 per cent. Hepatic artery flow fell only slightly with marked reduction in systemic flow. Thus, the observed decreases in total liver blood flow and oxygen consumption result almost entirely from decreased portal venous flow and oxygen content. The studies indicate that total hepatic blood flow and oxygen utilization of the liver are unimpaired at systemic perfusion rates of 2.2 ± 0.1 L. per minute per M.² or more.

Murmur of Mitral Stenosis with Sinus Rhythm

Weldon J. Walker, Frankfurt, Germany

An important factor contributing to the failure to recognize the characteristic murmur of mitral stenosis is the erroneous description of its timing in many current references. The late diastolic component or presystolic crescendo murmur, associated with atrial contraction, is well described.

On the other hand, the early murmur of mitral stenosis is often described as a mid-diastolic rumble, apparently related to the observation that a short period of isometric relaxation often separates the second heart sound from the opening snap and onset of the murmur. However, an analysis of the sound tracings from 37 patients with sinus rhythm and relatively pure mitral stenosis revealed that the diastolic rumble typically began in early diastole and characteristically reached its greatest intensity in the first and last thirds of diastole, correlating with the times of rapid ventricular filling. The murmur was usually less intense or even absent in mid-diastole. In only 2 of 37 tracings did the murmur reach maximum intensity in mid-diastole. For the most part, ventricular filling normally takes place in early diastole, and associated with this period of rapid ventricular filling is an early diastolic murmur, at times the first sign of mitral stenosis.

Accurate description of the timing of the characteristic murmur of mitral stenosis is essential in teaching students and physicians to recognize it. The concept that this murmur ordinarily starts in the mid-diastole is inaccurate and confusing.

Effect of Insulin Hypoglycemia on Plasma Epinephrine, Serum Nonesterified Fatty Acids (NEFA), and Blood Sugar in Normal Subjects

John M. Wallace and William R. Harlan, Durham, N.C.

That insulin hypoglycemia produces an increase in circulating epinephrine has not been convincingly demonstrated by direct measurement. Furthermore, relationships between blood glucose and epinephrine and clinical manifestations during hypoglycemia are unknown.

Six normal fasting men were given 45 units of regular insulin intramuscularly. Symptoms, blood pressure, and pulse rate, were observed and serial arterial blood samples were collected over a 2 hour period. In addition to glucose and epinephrine, NEFA were measured because of their sensitivity to both insulin and epinephrine activity. Quantitative epinephrine measurements were made with an ethylenediamine method, using 0.0020 μg . epinephrine per 5 ml. plasma as the standard. This gives 23 galvanometer deflections above the plasma alone. Duplicate 5 ml. plasma aliquots were used for each experimental determination.

Within 1 hour, NEFA fell to 51 per cent (455 μM . per L. to 236 μM . per L.) and glucose to 40 per cent (95 mg. per cent to 43 mg. per cent)

of controls. Epinephrine rose from a calculated value of 0.0005 μg . per 5 ml., to a measured level of 0.0087 μg . per 5 ml. During the next hour, NEFA rose to 70 per cent (319 μM per L.) and glucose to 54 per cent (51 mg. per cent) of controls; epinephrine partially fell to 0.0055 μg . per 5 ml. All figures are mean values. Symptoms appeared during maximum blood changes. Blood pressures and pulse rates of all subjects unexpectedly remained unchanged throughout.

Insulin hypoglycemia produced a marked increase in plasma epinephrine, which persisted for at least 2 hours and was accompanied by a tendency for the lowered NEFA and glucose to recover. Familiar symptoms appeared, but blood pressure and pulse were an unreliable index of circulating epinephrine during hypoglycemia.

Relative Contribution of Heart Rate and Stroke Volume to Changes in Cardiac Output in Man

Yang Wang, John T. Shepherd, and Robert J. Marshall, Rochester, Minn.

Cardiac output by the indicator-dilution method and heart rate were measured in 4 healthy untrained young men resting supine, standing, and walking at 1.7, 2.5, and 3.5 m.p.h. on a treadmill with a 12° tilt. Cardiac index averaged 3.6, 3.1, 6.4, 8.2, and 10.4 liters, respectively. Corresponding figures for heart rate were 66, 89, 122, 143, and 170; and for stroke index .55, .35, .52, .57, and .61 ml.

Thus the interpretation of changes in stroke volume with exercise depends on the reference point chosen. If this is resting supine, there is little change with exercise. Under these conditions, man resembles the dog in that changes in heart rate and not stroke volume account for most of the increase in cardiac output. From standing at rest, however, there is a marked increase in stroke volume with mild exercise and little further increase with severe exercise.

These findings agree with older observations and reconcile some of the apparent discrepancies in the literature concerning changes in stroke volume during exercise in man. Leg exercise in the supine position has been the basis of most of the previous observations on the changes of stroke volume with exercise in man.

Correlative Studies of Pulmonary Vascular, Airway and Alveolar Pressures During Spontaneous Positive and Positive-Negative Respiration

Watts R. Webb and Josef R. Smith, Jackson, Miss.

To evaluate the pulmonary circulatory effects of respiratory pressures in the open and closed chest with spontaneous and controlled respiration, pressures have been recorded in dogs in the pulmonary artery, pulmonary artery wedge, pulmonary venous wedge, left atrium, pleural space, and trachea. Also, a simple, direct method of continuously recording "alveolar" pressures—applicable both experimentally and clinically—by passage of a catheter into the bronchiolar "wedge" position allows correlation of the relative pressure changes at alveolar and capillary levels.

The alveoli are partially protected from positive tracheal pressures much as capillaries are from arterial pressures. Alveolar pressures parallel, without reaching the extremes, of positive pressures found in the trachea, whereas they more closely coincide during negative phases of mechanical ventilation. Alveolar and pleural pressures (esophageal pressures in man), while qualitatively similar, bear no definite quantitative relationship as they reflect different stresses.

The pulmonary artery wedge roughly parallels the left atrial and the pulmonary venous wedge the pulmonary arterial pressure changes, except at high airway and alveolar pressures where the opposite becomes true, demonstrating an alveolar-capillary block at an alveolar level of approximately 10-12 mm. Hg, which falls within the range of clinical anesthetic practices. In contrast, with early gentle, positive pressure, pulmonary artery wedge pressures fall. These and other derived curves support the concept that increasing airway pressures initially straighten and dilate the capillary bed with an enlarging extra alveolar space, but later can cause complete capillary compression despite the protective resistance of the bronchioles.

Use of a Simplified Oximeter Amplifier for Measurement of Oxygen Saturation and Dye Concentrations During Cardiac Catheterization

Max H. Weil, Los Angeles, Calif., and Robert B. Sudrann, Arcadia, Calif.

An oximeter amplifier (Ensco) originally described by Wiedhielm, used in conjunction with standard cuvette and earpiece (Waters), has been investigated for its applicability during routine cardiac catheterization. The instrument permitted immediate and continuous estimation of oxygen saturation of whole blood. The output of the amplifier was essentially a linear function of oxygen saturation or dye concentration. This provided considerable simplification of calibration.

Comparison was made between oxygen saturation values obtained with the oximeter and those

obtained on Van Slyke analysis of simultaneously collected samples. A calibration curve using Van Slyke samples was constructed for each patient. The standard deviation based on 77 samples was slightly less than 2 per cent saturation. Unpredictable variations in calibration values precluded use of a standardized calibration curve. However, the mean slope obtained from 11 calibration curves based on Van Slyke values was sufficiently constant to allow for a 1 point calibration using fully oxygenated blood, and thus requiring no Van Slyke measurements. This resulted in a standard deviation of differences of 2.3 per cent saturation between oximetry measurements and simultaneous Van Slyke values.

The unit has been used with standard cardiovascular recorders for performance of indicator dilution curves. This has permitted routine use of dye curves for detection of intracardiac shunts and valvular insufficiency, and reliable estimation of cardiac output.

Reliability and accuracy combined with added features of simplicity, low cost, conservation of space, and use of 1 instrument to perform a variety of measurements, has made this amplifier a valuable addition to our cardiac laboratory.

Familial Occurrence of Defects of the Interatrial Septum

Max H. Weil and Bertram J. Allenstein, Los Angeles, Calif.

Advances in heart surgery have allowed an increasing number of patients with major congenital heart lesions to reach reproductive age. This has renewed interest in genetic factors in the causation of congenital heart lesions.

The present study was based on 1 family, composed of the parents and 10 children. An interatrial septal defect was demonstrated in 4 members. The lesions were confirmed by cardiac catheterization in the father, aged 42, and 1 son, 13. In another son, 8, and a daughter, 16, definitive diagnosis was made at autopsy; each had interventricular as well as interatrial septal defect. Valvular pulmonic stenosis was present in both of the sons. The remaining 7 siblings were available for study. Each had a systolic murmur of moderate intensity in the area of the pulmonary artery. In 6 of the children, 1 of whom had cardiac catheterization, there was considerable doubt that this finding was associated with a major intra-cardiac abnormality. However, the youngest child, a girl aged 2, showed clinical signs suggesting interatrial septal defect and pulmonary stenosis. The mother, 38, paternal grandfather

and 3 of 4 paternal siblings had no evidence of heart disease on clinical examination. In 1 paternal aunt, the clinical findings were compatible with the diagnosis of a small left-to-right shunt at arterial level. Of incidental interest was the presence of abnormally high levels of serum cholesterol in members of this family.

Effect of Barbiturates on Coumarin Activity

Murray Weiner and Peter G. Dayton, New York, N.Y.

Wide variations in the clinical response to many drugs, and particularly the coumarin anticoagulants, are disturbing problems in the therapy of cardiovascular disease. Recent reports concerning adaptive enzyme mechanisms have led to renewed interest in the influence of some drugs on the physiologic disposition of others. These influences may account for some of the otherwise unexplained fluctuations in drug action. The following observations concern a model system for investigating this problem.

The effect of barbiturates on the prothrombin response to coumarins and the blood levels of coumarins was investigated under controlled conditions. Guinea pigs regularly responded to the intraperitoneal administration of 2 daily doses of 5 mg. acenocoumarin with marked hypoprothrombinemia. This response was eliminated by prior treatment with barbital, a drug which itself is excreted unchanged.

In human subjects the prior administration of heptobarbital markedly inhibited the prothrombin response to biseoumaacetate. This was correlated with a marked reduction in biseoumaacetate blood levels. In contrast, the same subjects showed no significant alteration in prothrombin response when heptobarbital was administered 5 hours after the biseoumaacetate. At that time most of the anticoagulant has already been eliminated, although the prothrombin response has not yet become apparent.

These data suggest that the inhibiting action of barbiturates, unlike that of vitamin K₁, is the result of alteration of the physiologic disposition of coumarin drugs. In the future, it may be necessary to pay more attention to the mutual influence of simultaneously administered drugs on their metabolic fate.

Psychology of Delayed Recovery in Coronary Thrombosis

Edward Weiss, H. Keith Fischer, Barney M. Lin, Samuel B. Hagner, George W. Russell, and William L. Winters, Jr., Philadelphia, Pa.

In a study of 63 patients, an effort has been made to determine the significance of emotional factors which precede, accompany, and follow coronary thrombosis. An introduction and general summary of the first 43 cases have been published.

Because the heart is the traditional seat of the emotions and is also the organ of sudden death, reactions to "heart attacks" may have special significance. The normal immediate reaction in a well-adjusted personality is some degree of anxiety and perhaps mood changes which last only a short time; as healing occurs, apprehension diminishes and symptoms disappear. Among the more persistent abnormal reactions, depression and denial are common. Although opposite in their outward manifestations, both are expressions of regressive (less mature) behavior and are related to the premorbid personality structure. The one is characterized by a preoccupation with symptoms, the other by a refusal to acknowledge the seriousness of the illness. Severe depression of spirits, poor sleep and hypochondriacal concern with symptoms occurred in 15 per cent of our cases. Although often masked by heart symptoms, it is important to recognize depression because it influences important decisions and poses the threat of suicide.

Denial, a reaction in which the patient acknowledges intellectually that he has had a coronary occlusion but behaves emotionally as though he has not, occurred in 14 per cent. Patients presenting the reaction of denial may jeopardize recovery by rash behavior. Treatment may necessitate less, instead of more, restriction.

The attitudes of physicians, nurses and family, particularly the spouse, are important in relation to recovery and rehabilitation.

Evaluation of the Use of Tracers for Detection of Cardiac Shunts and Valvular Incompetence

David Weitzman and Joan McAlister, London, England

Thirty patients with congenital or acquired heart disease were studied, using either radio-phosphorus or nitrous oxide during cardiac catheterization. P³² labeled red cells were injected into the pulmonary artery or right ventricle with simultaneous sampling from 2 right heart chambers. The nitrous oxide technic was as described by Morrow et al.

Nitrous oxide gave clear-cut results mainly in cases with large left-to-right shunts. With pulmonary hypertension and small shunts, differences in N₂O concentrations were no more significant than those in oxygen content, and of no more

help in localizing the defect. In some cases the N_2O content of mixed venous blood remained high for more than 15 minutes after cessation of inhalation; a longer time interval had to be allowed between serial investigations to avoid misinterpretation of figures.

Radiophosphorus proved more satisfactory for localizing congenital defects, since the technic demonstrates an interval of 10-15 seconds between arrivals of the tracer in shunt and pre-shunt chambers regardless of the magnitude of the shunt. P^{32} is useful also for detection of valvular incompetence provided this is significant and that a shunt can be excluded. A small leak may be missed because of "streaming" of the injection.

Serum Sodium and Potassium in Essential Hypertension

John M. Weller, Bernard E. Levine, and Richard E. Remington, Ann Arbor, Mich.

Some investigators have reported that there is an increased serum sodium concentration in patients having essential hypertension. It has also been postulated that an increased intake of sodium chloride in the diet is related to the development of essential hypertension. The present study was undertaken to evaluate further the relationships between stated dietary salt intake, determined serum sodium and potassium levels, and the existing level of the blood pressure.

Fifty normotensive and 43 hypertensive inpatients and outpatients have been studied. Data have been collected concerning age, sex, race, height-weight ratio, personal and hypertensive history, previous and present salt intake, blood pressure and serum sodium and potassium concentrations.

A preliminary survey of the data discloses no evident relationships between stated salt intake, serum sodium and potassium concentrations, or the level of the blood pressure. These variables are being subjected to rigorous statistical evaluation.

Nature and Identity of Thromboangiitis Obliterans

Stanford Wessler,† Si-Chun Ming, Victor Gurewich, and David G. Freiman, Boston, Mass.

The Beth Israel Hospital experience with thromboangiitis obliterans (TAO) yielded 84 patients with onset of arterial insufficiency prior to age 45. Since 36 of the 84 patients had clinical evidence of atherosclerosis or heart disease and were otherwise indistinguishable from the remaining 48 patients free of these conditions, no clinical criteria for the recognition of TAO could be derived from this study.

Arterial thrombi were found in specimens from all 18 patients in the study group with amputation. In only 8 of these 18 patients were the resected specimens free of atherosclerosis; moreover, 5 had clinical heart disease, atherosclerosis or arterial occlusion in the amputation stump and 3 who came to necropsy showed systemic embolization as a reasonable explanation of their peripheral arterial insufficiency.

Control studies established that the second and third stages of organization described by Buerger were nonspecific. No acute "specific" arterial lesion was observed, nor was documentation of such a lesion found in Buerger's published photomicrographs. Two acute "specific" venous lesions were found in our series and 5 additional such lesions were observed among a special group of outpatients.

Since these lesions occurred in the absence of clinical arterial disease, as well as in the presence of atherosclerosis and thromboembolism, the assumption that a specific arterial disease must exist in patients with this venous lesion is no longer tenable. It would appear that the disease labeled TAO is, in reality, the result of atherosclerosis or thromboembolism and that the term TAO should be discarded.

Observations on the Clinical Evaluation of Mitral Regurgitation

Richard N. Westcott, Cleveland, Ohio

Since the advent of the pump-oxygenator, clinical and preoperative evaluation of mitral regurgitation has presented an increasing responsibility to the cardiologist, especially in the selection of patients for conventional commissurotomy versus open repair of the mitral valve. Although numerous instrumental and highly technical methods of investigating mitral valve competence have been reported with varying success, it is our experience that the fluoroscopic findings of systolic expansion of the left atrium are a reliable sign of mitral regurgitation, particularly when correlated with other routinely available data. Although the somewhat questionable ultimate criterion of mitral valvular function has previously been the blind palpation of a regurgitant jet by the surgeon, direct visualization of the mitral valve during open cardiectomy has been possible in 19 patients operated on for mitral regurgitation at the Cleveland Clinic. The preoperative fluoroscopic observations correlated well with the operative findings in all but 1 patient with acquired disease where recognizable factors interfered with left atrial pulsations.

Effects of Hypophysectomy on Myocardial Function and Composition

William V. Whitehorn, Theodore M. King, and Billie Reeves, Chicago, Ill.

Previous observations of the role of gonadal steroids in regulation of function of cardiac muscle indicated significant reduction of contractility of surviving and glycerol extracted columnae carnae from ovariectomized albino rats. This functional effect was accompanied by proportionate reduction in ventricular actomyosin concentration. Estrogen administration resulted in recovery of normal values. Because of the well known role of pituitary factors in protein synthesis and the importance of pituitary-gonadal interrelationships, effects of hypophysectomy on contractility and composition of myocardium were studied. Maximum tension developed by surviving columnae of 8 hypophysectomized female rats was not different from that of 10 controls. Heart-body weight ratios were reduced in experimental animals. Total protein content of ventricle, actomyosin concentration and actomyosin as per cent of total protein were not modified by hypophysectomy in 9 animals compared with 9 controls. However, extracted contractile protein of the experimental group showed reduced viscosity drop with ATP addition. Results indicate significant differences between effects of castration and hypophysectomy on myocardial function and composition and suggest possible change in nature of contractile protein in the latter. Importance of pituitary-gonadal interplay in synthesis of cardiac contractile system is apparent.

Mitigation of Myocardial Depression Resulting from Elective Cardiac Arrest

Vallee L. Willman, Theodore Cooper, Panagiotis A. Zafiracopoulos, and C. Rollins Hanlon, St. Louis, Mo.

Ventricular function has been measured before and after elective cardiac arrest with cardiopulmonary bypass in 50 dogs. Stroke work was measured over a wide range of filling pressures altered by periodic infusion of blood.

Thirty minutes of elective arrest induced by potassium citrate, acetylcholine, anoxia, or a mixture of Prostigmin, magnesium sulfate and potassium citrate was found to result in a severe depression of function in the postarrest period. In these dogs, which weighed from 8 to 11 Kg., stroke work in the prearrest period varied between 25 and 50 gram meters. Following arrest, a stroke work of less than 10 gram meters was uniformly found.

Several measures to ameliorate this damage to the heart were studied. It was found that digitalis administered in the prearrest period or hypothermia of 28° provided some protection from the damage of arrest. With either of these measures, stroke work postarrest was between 15 and 20 gram meters.

The study permits several conclusions: 1. Cardiac arrest of 30 minutes in the dog during cardiopulmonary bypass is associated with a profound depression of myocardial function in the postarrest period. 2. Digitalization prior to elective cardiac arrest partially ameliorates the deleterious effect. 3. General body hypothermia of 28° also partially ameliorates this effect. The demonstrated depression of ventricular function following elective arrest may be a major factor contributing to mortality and morbidity following open heart surgery.

Laboratory and Clinical Evaluation of Double Dilution Curves in the Estimation of Valvular Regurgitation

William S. Wilson, Joe D. Morris, Ralph L. Brandt, and Edward W. Jenkins, Ann Arbor, Mich.

Valvular regurgitation was simulated in dogs by a shunt between the aorta and the central pulmonary artery. The shunt size was estimated by the increase in oxygen saturation in the pulmonary artery and by comparing the contour of indicator-dilution curves recorded simultaneously from the right ventricle and femoral artery after intravenous injection, according to the technic described by Lange and Hecht. A good correlation was found between the 2 technics in 12 determinations. The results are interpreted as providing evidence for the validity of the dilution method in the estimation of regurgitation, at least insofar as this preparation resembles valvular regurgitation.

In 38 patients, dilution curves were recorded from the pulmonary and femoral arteries after intravenous injection of indicator. The patients were divided into 4 groups by clinical, operative and pathologic criteria. In 18 patients classified as having no regurgitation, the mean ratio of regurgitation flow to forward flow (Q_r/Q_f) was 0.09. In 10 patients classified as having mild regurgitation, the mean Q_r/Q_f was 0.63. In 9 patients with moderate regurgitation, the mean Q_r/Q_f was 0.78. In 1 patient with severe regurgitation the Q_r/Q_f was 0.96.

It is concluded that an approximate, but useful, estimate of the degree of valvular regurgitation can be obtained with this method and that the technic might be of most value in excluding sig-

nificant regurgitation. The results in at least 1 patient indicate that in the presence of a large central volume, a falsely high estimate of the amount of valvular regurgitation may be obtained.

Evaluation of Anastomosis in the Coronary Circulation Resulting from Coronary Occlusion in the Miniature Pig

Martin M. Winbury, Edwin J. Hoff, Jr., Lorraine M. Hausler, and Lester Zitowitz, Bloomfield, N.J.

Previous investigators of the development of intercoronary anastomoses devoted little attention to the retrograde filling of the smaller vessels (arterioles). This study was designed to evaluate intercoronary anastomosis development following partial or complete occlusion of the left anterior descending (LAD) artery by quantitative grading of retrograde filling of (1) the artery and the main branches and (2) the smaller vessels (arterioles). The results indicate that it is essential to evaluate the finer detail of retrograde filling in order accurately to assess the functional significance of anastomosis development.

The diameter of the LAD was reduced 50-100 per cent under ether anesthesia; if fibrillation or failure developed, appropriate resuscitation measures were used. Animals with partial occlusion were re-entered in about 2 weeks and total occlusion performed. Corrosion casts were prepared after filling the right coronary artery and circumflex branch of the left coronary with vinyl acetate under pressure.

Filling of the smaller vessels occurs at a much later time after occlusion than does the main artery. At 0-2 days after occlusion there was no filling of the artery. At 6-16 days, 70 per cent of the animals (11) showed some filling of the artery, but only 30 per cent showed filling of the smaller vessels. Total occlusion resulted in greater filling than partial occlusion. After 21-210 days of occlusion, filling of the artery and smaller vessels was more extensive; there was some degree of filling of the artery in 80 per cent of the animals (6) and of the finer branches in 50 per cent. Two of 6 animals showed almost complete revascularization of the area.

New Basis for the Practical Application of Head-Foot Ballistocardiography to the Diagnosis of Heart Disease

Nahum J. Winer, New York, N.Y.

Method Rationale. Direct-body "acceleration" records higher frequencies of 20 or more cycles per second, detecting finer aberrations of body

movement and rendering such indeterminate factors as somatic structure and aging less significant. Head-foot recording, representing the major vector of forces, is usually sufficient. Corresponding heart sounds highlight subdivisions H_0 — H_L — J_R — J_L — J_D . Need for revision of system of grading seems necessary.

Three Types of Deterioration. 1. Functional deterioration: Relaxed breathing—attributed to "vascular pooling"—corrected by abdominal binder or suspended midinspiration; smoking—attributed to systemic vaso constriction—not coronary disease—corrected by ergot derivatives; decompensation—all predominantly affect IJK; delayed postexercise diminished amplitude with normal configuration. 2. Organic deterioration: Predominantly affects HI; premature atrial beats in the "low-reserve" heart; pulsus alternans—alternatingly; myocardial infarction—frequently with "M"-shaped IJK due to J_R — J_L dissociation—even with normal ECG. 3. Ischemic deterioration: A proposed clinical entity prodromal to myocardial infarction: "M"-shaped IJK of diminished amplitude, aggravated by exercise, with HI unaffected and ECG normal, particularly in younger adults with "tension anginoid personality" and systolic-diastolic hypertension; vasodilatation corrects these despite residual diastolic hypertension. Fibrosis of aging, or postinfarction—similar IJK but additional HI—predominantly amplitude diminution.

Aid in Cardiac Management. Differentiates between "high-" and "low-reserve" hearts: exercise could improve the former even with abnormal ECG; worsen the latter even with normal ECG. Determines gradation of activity in convalescence. Establishes the functional significance of electrocardiographic "insufficiency" in neurasthenia. Establishes vasodilator effectiveness. Establishes smoking sensitivity. May interdict nitroglycerin, causing deterioration due to excessive vasodilatation.

Occurrence of Pregnancy, Stillbirth, and Abortion Among Women with Coronary Artery Disease

Warren Winkelstein, Jr., and Albert C. Rekart, Buffalo, N.Y.

When the logarithms of the age-sex specific female death rates for arteriosclerotic heart disease (including coronary artery disease) are graphed, the rate of increase is almost uniform from age 30 years to age 60 years. If menopause delineated a period of lower susceptibility in early years and higher susceptibility in later years one would expect the rate of increase to change at menopausal age (40-50 years). The absence

of such an increase led to a comparison of the pregnancy experience of women with coronary artery disease with a suitable control group. Although this is an indirect way of assessing endocrine differences, it is relatively simple and provides a preliminary evaluation of the hypothesis that endocrine differences exist prior to menopause in women who develop coronary artery disease.

Data were obtained from 339 consecutive female admissions to the medical service of a large county hospital. Of these, 54 white women were postmenopausal and had a single diagnosis of arteriosclerotic heart disease or coronary artery disease, and 56 were postmenopausal with diagnoses other than cardiovascular disease. Diabetics were excluded from both coronary artery disease and control groups. Among 54 women with coronary artery disease, the age-adjusted proportion of abortions and stillbirths was 23.4 per cent, while among the 56 controls it was 14.5 per cent ($p = 0.05$). Patients with arteriosclerotic heart disease or coronary disease had a higher proportion of abortions and stillbirths in each 10 year age group over 50 years. There were too few Negro cases for analysis.

Pericardial Effusion in Congestive Heart Failure: Incidence and Significance

William L. Winters, Jr., Barbara L. Carter, Herbert M. Stauffer, and Louis A. Soloff, Philadelphia, Pa.

The enlarging cardiac silhouette which develops during congestive heart failure is attributed to cardiac dilatation. Cardiac dilatation is difficult and, at times, impossible to differentiate from pericardial effusion by conventional roentgenology. This study was initiated to determine if pericardial effusion may account for or contribute to the enlarging cardiac silhouette during failure.

Pericardial effusion was diagnosed when a thickened right atrial wall was visualized radiologically following intravenous injection of 100 cc. carbon dioxide in a manner previously described.

Thirteen patients, 6 males and 7 females, 37 to 71 years of age have so far been studied. Five had rheumatic heart disease, 4 hypertension, 3 coronary artery disease, and 1 heart disease of unknown cause. Four had obvious pericardial effusion, the extrapericardial density varying from 16-20 mm., 6 had no evidence of effusion, and 3 were doubtful, with the extracardiac density varying from 2-4 mm.

Retrospective study of the conventional cardiac silhouette failed to disclose features which could differentiate those with from those without pericardial effusion. Reduction of the size of the cardiac silhouette after compensation was restored may occur whether or not effusion had previously been present. The clinical picture also failed to differentiate these 2 groups although 3 of the 4 with effusion had rheumatic heart disease. Four plus edema up to the hips may be present without pericardial effusion, and conversely, pericardial effusion may be present with minimal peripheral edema.

Two of those with effusion died. Two without effusion died. One of the latter had rapidly progressive cardiac enlargement.

These preliminary studies suggest that pericardial effusion is due to local pericardial factors, perhaps antecedent pericardial disease, and may be more commonly present than is generally believed.

Peripheral Venous Distensibility in Essential Hypertension

J. Edwin Wood, Augusta, Ga.

The purpose of these experiments was to determine whether or not the vasoconstriction of essential hypertension involves the peripheral veins, as well as the peripheral arterioles.

The distensibility of the veins of the forearm was studied plethysmographically. This method measures the increase in volume of the veins of 100 ml. of forearm tissue when the effective venous pressure of these veins is raised from 1 to 31 mm. Hg — venous volume (30). The initial volume of the veins at 1 mm. Hg is low and constant. Thus, a small change in volume of the veins indicates constriction of veins relative to veins in which change in volume is large. Blood flow was measured concomitantly by the venous occlusion plethysmographic method. Arterial blood pressure was measured by the auscultatory method. Forearm peripheral resistance was calculated in arbitrary units by dividing mean arterial pressure by blood flow.

Ten untreated male patients with essential hypertension, having an average arterial blood pressure of 165/109 (range 138-208/92-136) mm. Hg, were studied 20 times. Their venous volume (30) averaged 35 (range 2.4-4.4) ml./100 ml. Their peripheral resistance averaged 38 (range 17-108) units. Fourteen normotensive male subjects were studied in the same manner 23 times. Their forearm venous volume (30) averaged 3.3 (range

2.4-5.4) ml. /100 ml. Their peripheral resistance averaged 25 (range 13-42) units.

These data indicate that the volumes of the forearm veins at a given venous pressure of hypertensive patients were not significantly different from those of normotensive individuals, despite a marked difference in forearm peripheral resistance in these two groups.

Blood Clotting Mechanism in Normal Young Males

Irving S. Wright and Margaret E. Todd, New York, N.Y.

Blood from normal young males was analyzed by the following tests: Glass and silicone clotting times, prothrombin complex, prothrombin consumption, partial thromboplastin tests, heparin tolerance, recalcification times, prothrombin and proconvertin tests, tests for factor V (AC globulin), factor VII (proconvertin), factor II (prothrombin) Stuart-Prower factor and anti-thrombin titers.

One hundred and six male students, age 22-30 years, have been screened. Abnormalities in 1 or more of the above tests were found in 15, or 14 per cent. Eleven, or 10 per cent, had abnormally shortened heparin tolerance tests. Two had abnormalities in the prothrombin complex (P and P) and factor VII tests. One had abnormal fibrinolysis. One student showed an unusual pattern of abnormality suggesting a bleeding tendency. These included prolonged coagulation times, both in glass and silicone tubes, reduced prothrombin consumption, abnormal thromboplastin as determined by the generation test, prolonged recalcification time corrected by normal plasma and a known hemophilic globulin deficient plasma. The heparin tolerance test was prolonged. The prothrombin complex time was normal, as were all of the factors concerned in this mixture (II, V and VII). In spite of these deficiencies, he has had a circumcision, appendectomy, tonsillectomy and adenoidectomy without bleeding complications. This suggests the Hageman trait. However, the patient's mother showed the same deficiency and she, too, has had surgery without hemorrhagic complications. This is believed to be the first case showing the inherited tendency of this trait.

If an incidence of approximately 14 per cent should persist as the size of the series is enlarged, this will constitute a very significant pattern of deficiency existing in the so-called normal population and will require further investigation.

Left Ventricular-Arterial Blood Volume in Valvular Heart Disease

Paul N. Yu, James K. Finlayson, Milton N. Luria, and C. Alpheus Stanfield, Rochester, N.Y.

In 29 patients with valvular heart disease radioisotope dilution curves were recorded from a systemic artery (FA) following injection into the left ventricle (LV) by Brock's percutaneous technic. In 14 patients, forward cardiac output was estimated by nearly simultaneous Fick procedure and this agreed closely with that determined by the dilution method. The LV to FA volume was calculated both by the Stewart-Hamilton method and Newman's slope formula.

The average LV to FA volume was 352 ml. per M.² in 7 patients with predominant mitral stenosis, 455 ml. per M.² in 2 patients with predominant mitral insufficiency, 416 ml. per M.² in 8 patients with predominant aortic stenosis and 458 ml. per M.² in 12 patients with predominant aortic insufficiency.

In patients with mitral or aortic stenosis, the LV to FA volume estimated by Newman's slope formula agreed closely with that calculated by the Stewart-Hamilton method. However, in patients with marked aortic insufficiency, the LV to FA volume by slope formula was usually greater than that by the Stewart-Hamilton method. A highly significant correlation existed between the LV to FA volume and the left ventricular diastolic pressure.

It is clear from these studies that the LV to FA volume is usually greater in patients with predominant aortic valvular disease than in those with predominant mitral stenosis, and that a larger LV to FA volume is present in patients with left ventricular decompensation. Provided there is no marked aortic insufficiency, the reciprocal of the downslope and mean transit time may be used interchangeably for estimation of the LV to FA volume.

Effect of Digitalis in Patients with Cardiomegaly without Congestive Cardiac Failure

Henry A. Zimmerman and Rodolfo S. Carballo, Cleveland, Ohio

Christian, in 1933, advocated using digitalis in patients with cardiomegaly in order to delay the onset of congestive failure. Stewart, in 1938, found variable results when 17 such patients were digitalized.

This study comprises 18 patients; 2 had normal sized hearts. Sixteen had enlarged hearts but were not in congestive failure by the following objective observations of normal: circulation time, venous pressure, right auricular and right ventricular diastolic pressures. The degree of enlargement varied from 5 to 25 per cent according to Ungerleider's tables. Six patients had hypertensive heart disease, 1 had cor pulmonale, 6 had rheumatic heart disease, and 3 had arteriosclerotic heart disease.

By means of intracardiac catheterization, the cardiac outputs and pressures were determined under basal conditions. Observations were made before and after 3 minutes of exercise. All patients received the same work load. The patients were then given 1.6 mg. of Cedilanid. After resting one hour, the cardiac outputs and pressures were restudied before and after 3 minutes of exercise.

Results. 1. When cardiac enlargement was less than 5 per cent, a decrease in the cardiac output occurred. 2. When cardiac enlargement was between 10 and 20 per cent, a minimal increase in the cardiac output at rest occurred. This increase was from .3 to 1.0 L. per minute. 3. When cardiac enlargement was greater than 20 per cent, a marked increase in resting and after exercise cardiac output resulted. This increase at rest was from .3 to 3.3 L. per minute and after exercise from 1.9 to 3.7 L. per minute.

Cardiomegaly above 15 per cent without congestive failure is an indication for digitalization.

Prevention of Ischemic Necrosis by Use of Levarterenol-Phentolamine Mixtures in Treatment of Shock

Gary Zucker, Robert P. Eisinger, Martin H. Floch, and Mark M. Singer, New York, N.Y.

The most commonly used type of vasopressor therapy in shock is the slow intravenous drip of

levarterenol. Accidental extravasation may lead to intense local vasoconstriction and cutaneous sloughs. Prevention is possible if the area is injected promptly with 5 or 10 mg. of the antiadrenergic drug, phentolamine. Neglect of the extravasation permits irreversible tissue damage. Extravasations frequently escape detection in spite of adequate medical and nursing supervision.

The routine addition of phentolamine to the flask of levarterenol automatically eliminates the danger from local vasoconstriction without impairing the hypertensive effect. Observations were made on 68 patients in shock. Good pressor responses were obtained with mixtures containing from 5 to 60 mg. of phentolamine and from 4 to 36 mg. of levarterenol. Thirty-three extravasations of mixtures occurred in 22 patients. None led to ischemia or necrosis. One extravasation of levarterenol alone resulted in the only slough in this study. It occurred in a patient who also had 2 extravasations of the mixtures. Neither of these led to necrosis. Our current conclusion is that 5 mg. of phentolamine added to a flask of levarterenol is sufficient to prevent necrosis in areas of extravasation. Rabbit experiments show that 2.5 mg. will protect against 8, 16, or 32 mg. of levarterenol. Further clinical studies are in progress to determine whether this dose or less will be equally effective in humans in shock.

SCIENTIFIC EXHIBITS

All Exhibits Will Be Displayed in the Convention Hall

Continuous, Indirect, Cuffless Recording of Blood Pressure. *Ralph H. Adams and Robert W. Corell, Wolfeboro, N. H.*

This exhibit shows how the electrical phenomenon of capacitance may be applied to measurement of pressure within an artery. The mechanics of transducer application to evolve a practical, non-constrictive, externally applied, nontraumatic, constant reading device are demonstrated.

(Booth S-6)

National Clearing House Program. *American Association of Blood Banks, Chicago, Ill.*

Describes functions and advantages of Clearing House Program for exchange of whole blood and whole blood credits between individuals and organizations. Exchange of credits is dramatized by an animated exhibit demonstrating usefulness of the program to physicians, patients and donors.

(Booth S-28)

Management of Refractory Heart Failure. *American Heart Association, New York, N. Y.*

The refractory state of heart failure calls for a systematic reappraisal of the patient's condition and previous treatment. The questions the physician has to answer cover the following basic areas: 1) What precipitated the failure? 2) What is the nature and extent of the condition? a) Lack of chemical equilibrium? b) Possibility of kidney failure? c) Noncardiac conditions confused with, or contributing to, heart failure? 3) What treatment has been used?

(American Heart Association Lounge)

Coronary Blood Flow and Hemodynamic Factors of Coronary Circulation. *Theodore A. Balourdas and John C. Scott, Philadelphia, Pa.*

Experimental studies were made on mongrel dogs by using the nitrous oxide desaturation method and establishing the coronary blood flow and the other determinants of coronary circulation. The experiments were performed in normal, vagectomized, atropinized, sympathectomized, hypothyroid and atherosclerotic closed-chest dogs. The results obtained in two runs for each experiment are exhibited.

(Booth S-22)

Shock and Arrhythmias: Their Management. *Arthur Bernstein, Jerome Kaufman, Frederick B. Cohen, Bernard Robins, and Franklin Simon, Newark, N. J.*

The treatment of shock, particularly that accompanying myocardial infarction, has been beset with many problems and complications. A new and practical method for managing shock in myocardial infarction and other conditions utilizing physiologic concepts will be presented. A new approach to the treatment of certain cardiac arrhythmias will be described with illustrative cases and pertinent electrocardiograms.

(Booth S-2)

Intercalative Angiography. *Robert J. Boucek, William P. Murphy, Jr., and Francisco Hernandez, Miami, Fla.*

A timer, excited by the R wave of the electrocardiogram, sets in motion, after a preset delay time (0.01 to 1.5 sec.), an injector delivering 3 to 30 ml. of radio-opaque substance through a cardiac catheter in 0.1 to 0.2 sec. and triggers a single x-ray exposure for discrete visualization of the cardiovascular system. X-ray pictures of ventricular cavities, the coronary system, congenital defects, and the equipment will be demonstrated.

(Booth S-18)

Anticoagulants and Clot Lysis. *Paul W. Boyles and Anwar A. Hakim, Miami Beach, Fla.*

Electrophoretic and chromatographic studies on purified coagulation proteins and their enzymatic alterations will be shown. Studies of intravenous fibrinolysin therapy on experimental blood clots in animals will be illustrated. The coagulation defects produced by long-term anticoagulant therapy and by intravenous fibrinolysin therapy in patients will be explained in relation to the coagulation reaction.

(Booth S-24)

Murmurs, Thrills, and Poststenotic Dilatation. *David L. Bruns and John E. Connolly, San Francisco, Calif.*

X-ray films on the 2 side walls show clinical and experimentally induced poststenotic dilatation. On the back wall, diagrams of previous theories of the cause of poststenotic dilatation will be compared with this present theory that murmurs, thrills, and poststenotic dilatation are interrelated. An apparatus inducing the same vibratory stress and dilatation in latex rubber tubes will be in operation.

(Booth S-9)

Rationale for Vasopressor Treatment of Shock. *Eliot Corday, Los Angeles, Calif., and John H. Williams, Boston, Mass.*

This exhibit will demonstrate the effect of shock and vasopressor drugs on the circulation of the brain, myocardium, liver, G.I. tract and kidney, but increase the blood flow of the brain, myocardium and liver.

(Booth S-12)

Hypothermia in Clinical Medicine. *R. Adams Cowley, Emil Blair, Paul Hackett, and John Allen, Baltimore, Md.*

The exhibit demonstrates: (1) the range of clinical usefulness of hypothermia, including cardiovascular surgery (hypothermia alone or with the pump-oxygenator), septicemia, shock, renal shutdown, and neurosurgery; (2) indications, protocol of management, temperature ranges, pitfalls and results; (3) clinical physiology; (4) recent research; and (5) future possibilities.

(Booth S-11)

Surgical Considerations in the Treatment of Cerebral Arterial Insufficiency. *E. Stanley Crawford, Michael E. De Bakey, William S. Fields, George C. Morris, Jr., and Denton A. Cooley, Houston, Tex.*

In our experience, the occlusive lesion in patients with cerebral arterial insufficiency is located in the neck or chest in approximately 40 per cent of the cases. Although various patterns of involvement may occur, the lesions, being multiple in 50 per cent of the cases, are located in the innominate, common carotid, subclavian, vertebral and internal carotid arteries. These lesions, being frequently segmental in nature and extracranial in location, are susceptible to certain procedures designed to restore normal circulation. This exhibit is concerned with the diagnosis, pathology, and surgical treatment of 100 occlusive lesions in vessels, as indicated above. Normal pulsatile blood flow was restored in the majority of these patients and the functional results were equally as gratifying.

(Booth S-25)

Prolonged Veno-Arterial Pumping for Circulation Support. *James F. Dickson, III, James W. Dow, and Neil A. J. Hamer, Philadelphia, Pa.*

In acute reversible conditions with a diminished cardiac output, such as in myocardial infarction, mechanical support of the circulation for a number of days may be beneficial. A closed system for veno-arterial pumping is exhibited that has been employed experimentally for as long as 52 hours, and clinically for 26 hours, without ill effect.

(Booth S-1)

Experiences with the Anticoagulant Phenprocoumon. *Robert E. Ensor and H. Raymond Peters, Baltimore, Md.*

Our results with phenprocoumon in 5,000 patients, from June 1955 to March 1958, are shown. A comparison with other drugs and practical points in the clinical use of this drug are presented. Graphs, showing the characteristic type responses are demonstrated. The greater predictability of response and stability of the prothrombin curve have sustained our interest in this drug.

(Booth S-3)

New and Simplified Method of Electrocardiographic Interpretation, Using the Vectorelectrocardiogram, or V-ECG. *J. Louis Freibrun, Julien H. Isaacs, Willard J. Zinn, and George C. Griffith, Los Angeles, Calif.*

The vectorelectrocardiogram (V-ECG) is an electrocardiographic record of the spatial data contained in the vectorecardiogram. A simplified method of analyzing the V-ECG translates vector data directly into physiologic and pathologic equivalents. Over 2,000 V-ECG's have been correlated with the routine electrocardiogram and extensive clinical, physiologic and pathologic findings.

(Booth S-10)

Cardiac Valvular Dynamics. *Robert P. Glover, Julio C. Davila, Robert G. Trout, R. Philip Custer, and Joseph Sumner, Philadelphia, Pa.*

The Presbyterian Pulse Duplicator is an apparatus making possible the graphic study of the normal and diseased cardiac valves functioning under conditions which duplicate living cardiovascular dynamics. In the field of research, it has proved useful for the study of valvular mechanics, the investigation of problems in circulatory dynamics simulated in vitro and in the development of advanced corrective operations applicable to valvular heart disease.

(Booth S-4)

Nonsuture Internal Mammary-Coronary Artery Anastomosis. *Robert J. Hall, Edward M. Khouri, and Donald E. Gregg, Washington, D. C.*

Anastomosis of the internal mammary artery to the circumflex branch of the left coronary artery in dogs is described. The method, employing a cuff of nylon or stainless steel is simple, direct and yields a high incidence of widely patent anastomoses after a 1 year follow-up. Data are presented on flow through the anastomosis measured by the electromagnetic flow meter.

(Booth S-21)

Streptococcal Infections and Rheumatic Fever: Specific Therapy. *Harold B. Houser, Floyd W. Denny, Jr., Edward A. Mortimer, Jr., Charles H. Rammelkamp, Jr., and Ralph J. Wedgwood, Cleveland, Ohio*

The natural history of streptococcal infections, rheumatic fever, and rheumatic heart disease in 1,000 children is shown. How this natural history can and should be interrupted by the proper employment of penicillin at various points in the natural history is illustrated.

(Booth S-5)

Lymphangiography. John M. Howard, Robert Bower, and Edward Ehrlich, Philadelphia, Pa.

A technic for identification of lymphatic vessels by subcutaneous deposition of patent blue dye is shown. Lymphangiograms obtained after injection of a radio-opaque medium directly into peripheral lymph vessels are demonstrated. A number of pathologic states characterized by peripheral edema, such as primary lymphedema, postphlebitic syndrome, varicose syndrome, cardiac and hepatic disease, and postsurgical edema are included.

(Booth S-27)

Surgery of Acquired and Congenital Heart Disease.

Earle B. Kay, David Mendelsohn, and Henry A. Zimmerman, Cleveland, Ohio

An exhibit is proposed, illustrating with transparencies and motion pictures the acquired and congenital lesions of the heart and great vessels of the thorax. Special emphasis as to indications and the opportune time for cardiac evaluation and surgical intervention of the various cardiac conditions will be stressed.

(Booth S-23)

Nonpenetrating Injuries of the Heart and Aorta.

William C. Manion, Thomas W. Mattingly, Loren F. Parmley, Jr., and Edward J. Jahnke, Jr., Washington, D. C.

The exhibit consists of 3 panels entitled: "Pericardial and Myocardial Injuries," "Causation and Pathology," and "Aortic Injury and Rupture." It shows, in a series of cartoons, the primary causes of nonpenetrating injuries of the heart and aorta. Clinical and pathologic aspects of 546 cases of nonpenetrating cardiac injury, and 275 cases of traumatic aortic rupture, are presented by illustration of pathology specimens, roentgen studies, electrocardiographic data, and case histories.

(Booth S-7)

Estrogen in the Prophylaxis of Atherosclerosis and Myocardial Infarction. Jessie Marmorston, Oscar Magidson, Oliver T. Kuzma, Frederick J. Moore, Al White, Jack J. Lewis, Shawn Shapiro, Sheldon Rosenfeld, Ross Jacobs, and Sara Myers, Beverly Hills, Calif.

This exhibit summarizes: (1) our clinical experience with the administration of small and moderate

dosages of estrogen to men and postmenopausal women with myocardial infarction; and (2) the effects of estrogen administration in dogs which have been made atherosclerotic by thyroidectomy plus cholesterol administration, or by thiouracil plus cholesterol administration. Pathologic specimens will be included.

(Booth S-17)

A-V Dissociation and "Interference." Henry J. L. Marriott, Harold H. Bix, Adalbert F. Schubert, Gerard Church, and Samuel M. Bradley, Baltimore, Md.

Varieties of A-V dissociation (momentary, interference-dissociation, isorhythmic, etc.) are illustrated; the differing and conflicting usages of "interference" are diagrammed. A model with sliding panels, demonstrating the changing relationship of atrial to ventricular impulses during dissociation, clarifies the concept of "zones" of interference, dissociation and fusion.

(Booth S-13)

Pulse Volume and Perfusion Flow From Electrical Conductances: Radio-Frequency Impedance Plethysmography. Jan Nyboer, Detroit, Mich.

Flow of blood is calculated from the pulsatile impedance values. Pulses of increased electrical conductance with systole occur outside the cardiac region. However, a decrease in conductance occurs directly over the heart. The pulse is modified by arterial and venous hindrance to flow, as well as by the delivered volume.

(Booth S-19)

Tilt Table Studies in Zero Gravity. Robert N. Olson and Leonard J. Stutman, Dayton, Ohio

This experiment was designed to study the physiologic effects of entry into and re-entry from the zero gravity field. The tilt table and recording devices will be demonstrated in the exhibit, as well as pictures of the flying laboratory and examples of recordings taken during flight.

(Booth S-20)

Is Auscultation a Lost Art? Test Your Diagnostic Ability. Edmund H. Reppert, Jr., and J. Scott Butterworth, New York, N. Y.

This is a series of 15 common conditions which are sufficiently typical to be diagnosed by auscultation alone. The recordings are on tape and are played back through individual stethophones and at the same time the visual pattern can be seen on large oscilloscopes. The test will be corrected immediately and returned to the individual. No names or other identification are required.

(Booth S-26)

Transseptal Left-Heart Catheterization. *John Ross, Jr., Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.*

The exhibit demonstrates the technic and applications of a new method of left-heart catheterization. The interatrial septum is punctured with a flexible needle inserted through a cardiac catheter positioned in the right atrium, and the left ventricle and aorta are entered with a fine plastic catheter passed through the needle.

(Booth S-14)

Effect of Intradermal Serotonin on Peripheral Vasomotor Reactivity. *Arthur L. Scherbel, John W. Harrison, and Victor G. deWolfe, Cleveland, Ohio*

An exaggerated reaction to intradermal serotonin occurs in patients with Raynaud's disease, secondary Raynaud's phenomenon and diseases of the connective tissue system. Examples are shown and compared with controls by means of color photography. The technic for performing the serotonin skin test to provoke vasomotor reactivity is described and discussed.

(Booth S-8)

Experimental Coronary Arteriography. *W. H. Shuford, W. H. Sewell, and Pablo A. Davalos, Atlanta, Ga.*

This exhibit presents various methods of coronary arteriography evaluated in the dog. Temporary cardiac arrest by acetylcholine has been found to be the most satisfactory, and this technic will be described in detail. Arteriograms demonstrating both normal and disease states of the coronary arterial system will be shown.

(Booth S-15)

Coronary Angiography in Arteriosclerotic Heart Disease. *Alan P. Thal, T. Tamiya, R. Greenspan, and M. J. Murray, Minneapolis, Minn.*

Coronary arteriograms of a number of patients with proven coronary artery disease will be demonstrated. The sites of occlusion and collateral response to ischemia will be shown. In addition, several examples of an erroneous clinical diagnosis of coronary disease are represented. The injection system will be assembled and demonstrated.

(Booth S-16)

INDUSTRIAL EXHIBITS

All Exhibits Will Be Displayed in the Convention Hall

Advanced Instruments, Inc., Newton Highlands, Mass.

(Booth 14). For ultra-precise 0.002 pH, the new Vibron pH Electrometer; electrodes for anaerobic blood, and, if ready, pCO₂ and Na⁺. For precise Na⁺ and K⁺, the new, high-stability Advanced Flame Photometer. Smallest instrument, featuring big-instrument repeatability. For precise osmolality, the proven, widely-used, direct-reading Fiske Osmometer. \pm mOsm repeatability. Sample sizes down to 0.2 ml.

Atronic Products, Inc., Bala-Cynwyd, Pa. (Booth 19).

Atronic Pacer Monitor. A new battery-operated and transistorized Monitor is presented. This instrument combines an artificial cardiac stimulator, a meter display of the heart's electrical activity, and a test of the electrical connection to the heart. A new high-strength flexible wire electrode for percutaneous connection to the heart is demonstrated. The Atronic Pacer was developed in conjunction with the Department of Cardiology at the Philadelphia General Hospital.

C. R. Bard, Inc., Summit, N. J. (Booth 47) will feature Teflon Knitted and Woven Arterial Grafts, Teflon Interlocking Mesh for Tissue Repair, Cardiovascular and Venous Catheters and Bardic Deseret Intracath.

Becton, Dickinson and Company, Rutherford, N. J.

(Booth 53) cordially invite you to visit their exhibit of special B-D products for heart catheterization and heart surgery. Among the items will be rotating adapters, stopcocks, animal tested medical grade tubing in both vinyl and polyethylene. Also on display will be especially designed needles by medical specialists.

Birtcher Corporation, Los Angeles, Calif. (Booth 65).

They will exhibit their entire line of cardiac instruments, consisting of the following: Dual Speed Electrocardiograph, Cardioscope, Defibrillator, Heartpacer, Dual Trace Electronic Switch, and E. E. G. Pre-Amplifier. All these instruments are mounted on a 5' Mobile Pyramid Cabinet, forming a complete and self-contained mobile cardiac monitoring and resuscitation center.

Blakiston Division, of McGraw-Hill Book Co., Inc., New York, N. Y. (Booth 48) will exhibit the following books: *Cardiology—an Encyclopedia of*

the Cardiovascular System, sponsored by the American College of Cardiology, and edited by Aldo A. Luisada; the Glover Clinic's *The Practical Evaluation of Surgical Heart Disease*; White, Rusk, Lee, and Williams' *Rehabilitation of the Cardiovascular Patient and Cardiovascular Rehabilitation*; A.M.A. *Handbook on Standard Nomenclature of Diseases and Operations*; Stead and Warren's *Low-Fat Cookery*.

Bowen & Company, Inc., Bethesda, Md. (Booth 11)

will display Calibrated Ballistocardiograph, Smith-Perls Model, Welsh Self-Retaining Electrodes, standard and infant sizes, Krasno-Graybiel Metal Plastrodes, requiring no electrode paste, Howel Electrode, self-retaining, with electrolyte retaining ridges, especially for use with liquid and cream solutions, QT Calculator for determining the QTc or the QT Ratio, and a Liquid Dispenser for use with alcohol and other cleansing liquids.

Bristol Laboratories, Inc., Syracuse, N. Y. (Booth 42).

You are cordially invited to visit their booth, where Saluron, a new and improved oral diuretic, developed by Bristol Research Laboratories, will be introduced. Saluron is sustained-action hydroflumethiazide. It induces 18-hour diuresis with a single 50-mg. tablet, with minimal risk of potassium and bicarbonate depletion.

Burdick Corporation, Milton, Wis. (Booth 60) will

exhibit their new dual speed direct-recording electrocardiograph, Model EK-3, and their Telecor for cardiac monitoring during surgery. Representatives from their engineering and sales departments will be on hand to discuss this equipment with the doctors attending the convention.

Burroughs Wellcome & Co. (USA), Inc., Tuckahoe,

N. Y. (Booth 44). Their extensive research facilities, both here and in other countries, are directed to the development of improved therapeutic agents and technics. Through such research they have made notable advances relating to leukemia, malaria, diabetes, and diseases of the autonomic nervous system, and to antibiotic muscle-relaxant, antihistaminic, and anti-nauseant drugs. An informed staff at their booth will welcome the opportunity to discuss their products and latest developments with you.

Cambridge Instrument Co., Inc., New York, N. Y. (Booths 30 and 31) will exhibit *Multi-Channel Units* for recording and monitoring various physiologic and biophysics phenomena; their *Versa-Scribe*, the versatile portable electrocardiograph; *Explosion-Proof Operating Room Cardioscope* for use in the operating room and also in monitoring experimental phenomena (with remotely-operated *Simpli-Scribe Direct-Writing Portable Electrocardiograph*); *Audio-Visual Heart Sound Recorder* for the study of the teaching of auscultation; *Research pH Meter*; *Pulmonary Function Tester*; and *Gamma Ray Pocket Dosimeter*. Their engineers in attendance will be glad to give complete information on these instruments and to discuss any instrumentation requirements.

Carnation Company, Los Angeles, Calif. (Booth 15) cordially invite you to visit their booth where medical specialist representatives will be pleased to welcome old and new friends. Recent literature and information regarding *Carnation Evaporated*, *Instant Non-Fat*, and their newest product, *Carnalac*, are available. Any question pertaining to their physician-researched material for use in your practice or hospital will be cheerfully discussed.

Ciba Pharmaceutical Products, Inc., Summit, N. J. (Booth 12). *Esidrix* is hydrochlorothiazide, an improved analog of chlorothiazide. It is a powerful oral diuretic-antihypertensive drug. Therapeutically, *Esidrix* is 10 to 15 times more potent than chlorothiazide. Weight losses up to 56 pounds have been reported. In many cases, *Esidrix* caused copious diuresis in patients unresponsive to other oral and/or parenteral diuretics. Side effects are usually mild, infrequent and readily controlled.

Coca-Cola Company, Atlanta, Ga. (Special Area). Ice-cold Coca-Cola served through the courtesy and cooperation of the Philadelphia Coca-Cola Bottling Company and the Coca-Cola Company.

Corco Incorporated, Culver City, Calif. (Booth 67). *Kay-Anderson Heart-Lung*, featuring the automatic filmer. Three completely autoclavable models: 10-screen size for pediatrics, 16-screen size for general use, 20-screen size for use where a greater amount of perfusion is required. Each model is versatile, since the number of screens may be varied from 1 to maximum, as desired.

Darwin Laboratories, Los Angeles, Calif. (Booth 59). *LH 400 (Lipo-Hepin)*, sodium heparin, U.S.P. 400 mg. per cc., allows a significant increase in

efficiency of anticoagulant and lipoprotein lipase response. Administration and control problems, usually associated with heparin therapy, are essentially eliminated. Other heparin concentrations and other products will be discussed.

Davies, Rose & Company, Ltd., Boston, Mass. (Booth 18). Although most physicians need no introduction to their outstanding cardiac therapies, *Pil. Digitalis* and *Tablets Quinidine Sulfate (Natural)*, their representatives will be on hand to welcome you and to explain the dependability of their laboratory productions.

Electrodyne Company, Inc., Norwood, Mass. (Booth 63). On display will be the latest medical equipment dealing with the prevention, detection and treatment of cardiac arrest, including the *Electrodyne PM-65* with *Electrocardioscope*, which provides for automatic and instantaneous external stimulation should arrest occur. Also featured is their *Electrodyne D-72 External Defibrillator* and the *Miniature Transistorized Cardiac Pacemaker*, which operates either on battery or electricity. Their representatives will be pleased to demonstrate these instruments at their booth.

Electro Medical Research Associates, Inc., Schenectady, N. Y. (Booth 28). *Cardio-Axiograph*, a new measuring instrument for direct reading of the electrical heart axis. *Electro-pulsometer*, an electronic indicator and continuous recorder of pulse-rate. *Biological OHM Meter*, an auxiliary meter for cardiology.

Electronics for Medicine, White Plains, N. Y. (Booths 23 and 24). Several types of multichannel monitoring and recording systems for cardiac research and diagnosis, surgery, and recovery room will be shown. The *Model PR-4* is a new instrument for vector and 4-channel scalar recording. The *ORM-1* is a compact and explosion proof monitor for ECG and EEG during surgery.

Encyclopaedia Britannica, Inc., Philadelphia, Pa. (Booth 29), will feature their 1959 edition. This new edition is described as "The most up-to-date, complete and exhaustive, authoritative reference library published." You are invited to participate in a dynamic new program.

Endo Laboratories, Inc., Richmond Hills, N. Y. (Booth 66) will present the following therapeutic preparation which merits your interest: *Coumadin sodium*, anticoagulant, may be administered parenterally, as well as orally, and provides predictable therapeutic cover with fewer "escapes."

Coumadin permits both acute and long-term anticoagulation with less frequent prothrombin time determinations.

Foregger Company, Inc., Roslyn Heights, N. Y. (Booth 87) will exhibit the *Pulspirator*, a new apparatus for use in open-heart surgery which takes over the function of the heart and lungs during thoracic operations. It is the result of 3 years of developmental work and operates entirely without electrical supply. It has been used successfully in more than 20 cases.

E. Fougera & Company, Inc., Hicksville, N. Y. (Booth 39). For both initial digitalization and maintenance therapy, the steady predictable effect of *Digitaline Nativelle* facilitates individualized treatment for any cardiac patient. Complete absorption from the intestinal tract and uniform dissipation of *Digitaline Nativelle* permits easy attainment and maintenance of optimal effects. Available in oral, intramuscular, and intravenous form with weight-for-weight equivalence of dosage.

Geigy Pharmaceuticals, Yonkers, N. Y. (Booth 86) cordially invite you to visit their technical display. Information on products valuable in therapy of rheumatic, metabolic, dermatologic and cardiovascular diseases will be presented by personnel in attendance.

General Foods Corporation, White Plains, N. Y. (Booths 26 and 27). New *Aroma-Roast Instant Sanka Coffee* will be served. It is 100 per cent pure coffee but 97 per cent of the caffeine has been removed for patients who need less caffeine. You are invited to visit their booth to register for professional samples and a supply of leaflets on caffeine. *Sanka Coffee* will also be displayed.

Gilford Instrument Laboratories, Inc., Elyria, Ohio (Booth 51) will display their new infrared *Densitometer* for use with *Fox Green*. A new linear instantaneous cardiometer, based on a new principle and displaying pulse rate directly in numerical form, will be demonstrated. Pulse information can be picked up from the subject by earpiece, finger-tip pick-up, blood pressure cuff, or ECG with standard attachments. A new low resistance spirometer also will be on display suitable for measurement of maximum breathing capacity and other pulmonary functions. Results are immediately displayed in numerical form. Their *Model 110 Automatic Blood Pressure Recorder* will be demonstrated; it permits

measurement of systolic or diastolic pressure approximately every 3 to 4 seconds.

Grune & Stratton, Inc., Medical Publishers, New York, N. Y. (Booths 79 and 80). Their representative will be on hand to show you their newest titles, such as *Tocantins' Progress in Hematology, Volume II*; *Adams & Veith's Pulmonary Circulation*; *Kossmann's Advances in Electrocardiography*; *Wiggers' Reminiscences and Adventures in Circulation Research*; *Wright-Millikan's Cerebral Vascular Diseases*; *Thannhauser's Lipidoses*; the new quarterly journal, *Progress in Cardiovascular Diseases*, edited by Charles K. Friedberg; *Saphir's A Text on Systemic Pathology* (now complete in 2 volumes); and *Scherf & Boyd's Cardiovascular Diseases*. Also many other important books and journals which you are invited to inspect.

Hiss Pharmacal Co., Inc., Utica, N. Y. (Booth 83), will feature *Vasotrate Unicelles*, 30 mg., No. 1, and No. 2, for the prevention of recurrent angina attacks; *Tenamine Unicelles*, for the treatment of hypertension, and as a mild tranquilizer; and *Liparin Injection*, used in diseases associated with impaired lipid metabolism. Representatives will be at the booth to service the physicians.

Paul B. Hoeber, Inc., New York, N. Y. (Booth 82), publishers, invite members to visit their display of medical books. Among the books of particular interest to members are *Rosenbaum and Belknap's Work and the Heart*, *Plotz' Coronary Heart Disease*, *Bayley's Electrocardiographic Analysis*, and *Gardberg's Clinical Electrocardiography*.

Lea & Febiger, Philadelphia, Pa. (Booth 61). You are welcome to examine these new books and current standard titles: *Goldberger, A Primer of Water, Electrolyte and Acid-Base Syndromes*; *Katz, Stamler and Pick, Nutrition and Atherosclerosis*; *Master, Moser and Jaffe, Cardiac Emergencies and Heart Failure*; *Katz and Pick, Clinical Electrocardiography*; *Goldberger, Heart Disease*; *Goldberger, Unipolar Lead Electrocardiography and Vectorcardiography*; *Burch and Winsor, Primer of Electrocardiology*; *Burch, Primer of Cardiology*; *Burch Abildskov and Cronvick, Spatial Vectorcardiography*; and many other books of interest.

Thos. Leeming & Co., Inc., New York, N.Y. (Booth 32). *Metamine Sustained* for the prevention of angina pectoris will be featured. Physicians not already

familiar with *Metamine Sustained*, the unique coronary vasodilator in b.i.d. dosage, are urged to visit the Leeming booth for full chemical, pharmacologic and clinical information. Also *Metamine Sustained* with *Reserpine* and *Metamine* with *Butabarbital Sustained*.

Eli Lilly & Company, Indianapolis, Ind. (Booths 35 and 36) will feature *Ilosone TM*, propionyl erythromycin ester; *Cytellin*—sitosterols; *Crystodigin*—crystalline digitoxin; and *Potassium Triplex*.

Mark Company, Randolph, Mass. (Booth 41) will present a complete mechanical heart-lung apparatus of the very latest design in operation with automatically monitoring pH and oxygen electrodes and additional latest automatic features now commercially available in this field. Other items will include heart defibrillators, pace-makers, blood and oxygen flowmeters, special mobile perfusion pumps, etc.

Merck Sharp & Dohme, Philadelphia, Pa. (Booths 33 and 34) will feature *Hydrodiuril*, a new, orally effective, nonmercurial diuretic-antihypertensive agent. This compound is a very potent diuretic agent, equaling or exceeding the potent parenteral organomercurials in diuretic activity. Like *Diuril*, the principal action of *Hydrodiuril* is a marked enhancement of the excretion of sodium and chloride. Technically trained personnel will be present to discuss these and other subjects of clinical interest.

Micro X-Ray Recorder, Chicago, Ill. (Booth 55). A comprehensive collection of 2" X 2" Medical Teaching Slides in 13 series (to date) on heart and chest will be featured. These, as well as other series, will be available for viewing on their Recorder Projector-Viewer. This unit will project 2" X 2" slides and 35 mm. film for teaching and lecture without burning or buckling even cardboard mounted slides.

C. V. Mosby Company, St. Louis, Mo. (Booth 37). New knowledge, ideas, research and technic are available for your inspection in the new books published in 1958 and 1959. Their representative will be happy to discuss any book with you.

Nordson Pharmaceutical Labs., Inc., Irvington, N. J. (Booth 52). *Ergomar* is a new form of specially processed ergotamine tartrate, specifically for sublingual administration in the treatment of recurrent and throbbing type vascular and mi-

graine headache. Bypassing the gastric and hepatic enzymatic barriers, *Ergomar* insures more rapid relief and avoids gastric upset. Also featured is *Levonor*, the nonstimulating appetite suppressant. *Levonor's* smooth action permits its use even during the late evening hours without disturbing sleep. Latest reprints are available on *Ferronord Liquid* and tablets, a chelate hematinic, providing rapid hemoglobin response without side effects.

North American Philips Co., Inc., New York, N. Y. (Booth 88) will feature a reproduction of an actual Cardio-Pulmonary Laboratory, set up for cardiac catheterization and angiocardiology, with their Heart Catheterization Table, their new 9" Image Intensifier, Cine recording devices in both 16 mm. and 35 mm., Closed Circuit TV, and complete processing and projection equipment.

Ortho Pharmaceutical Corporation, Raritan, N. J. (Booth 54). The opening of a new epoch in medical therapy is represented by *Actase Fibrinolysin (Human)*, the newly released blood clot lysing agent. Indicated specifically in thrombophlebitis and pulmonary embolism, *Actase Fibrinolysin (Human)* is a naturally derived blood fraction which they are proud to present in their exhibit.

Oxy-Lyfe Corporation, Chicago, Ill. (Booth 64) will feature their Portable Oxygen Units. Five models varying in duration from 30 minutes to 2 hours and 30 minutes. Each unit includes carrying case, cylinder pressure gage, regulator, 3 ft. length of tubing, and comfortable face mask. Extremely light, portable, and easy to use.

Picker X-Ray Corporation, White Plains, N. Y. (Booth 38) will show a complete cardiological x-ray unit. This provides facilities for TV, remote viewing and synchronized cineradiography at 60 frames per second. This is the first such unit designed exclusively for fluoroscopic studies of the heart.

Roche Laboratories, Div. of Hoffmann-LaRoche, Inc., Nutley, N. J. (Booth 25). *Marsilid* is a psychic energizer—the very opposite of a tranquilizer. *Marsilid* has a pronounced therapeutic effect in depressed and regressed psychotic patients, in mild depression, as an appetite stimulant, and in promoting increased vitality.

Sanborn Company, Waltham, Mass., (Booths 57 and 58) will display a wide selection of instruments for biophysical research—some in simulated operation to aid understanding of function and operating features. They will also include Recording

Systems (single and multichannel, direct writing, photographic and tape). Monitoring Oscilloscopes, Transducers (pressures, temperature, etc.) and new Preamplifiers, which permit wide range of physiologic applications. Visitors are cordially invited to see these latest models and to discuss technical problems with their representatives.

Sandoz Pharmaceuticals, Hanover, N. J. (Booth 56).

Cedilanid is a pure glycoside (lanatoside C) of digitalis lanata with quick onset of action, quick excretion, and a low toxicity useful for i.v. administration in cardiac emergencies. Acylanid has all the advantages of digitoxin but the safety of whole leaf digitalis.

Schick X-Ray Co., Inc., Dis. for Elema-Schonander, Chicago, Ill. (Booth 13).

Their line of equipment will include: direct-writing jet recorders for ECG, phonocardiography, pressure, etc., film-changers for angio-cardiography, high pressure injection syringes, and fluoroscopic tables for catheterization, etc.

Schiffelin & Company, New York, N. Y. (Booth 62)

will exhibit C.R.P.A. (C-reactive Protein Antiserum), a unique diagnostic aid for the detection of inflammatory diseases. This practical and simple test brings your patient's hidden inflammation to light. Unlike the E.S.R., there is no normal range. It is either negative or positive. The quantity of the precipitate reflects the severity of the condition. The precipitate diminishes as therapy reduces inflammation. Danilone, the oral anticoagulant of choice, has been found to possess decided clinical advantages over other anticoagulants in the therapy and prophylaxis of thromboembolic diseases. Representatives will be on hand to discuss these advantages.

Schwarzer Company, Boston, Mass. (Booth 43)

will present and demonstrate some of their Cardio-script models. These are multipurpose direct-writing instruments for the recording of: phonocardiograms (up to 2,500 c.p.s. in 6 selective filters), ECG, EEG, pulse tracings, pressures, oximetry, dye dilution measurements, ballistocardiac vectorcardiograms, blood flow estimations, etc. Also on display will be the portable Cardio-script III.

G. D. Searle & Co., Chicago, Ill. (Booth 85)

will feature Dartal, the new tranquilizing agent which controls activities associated with anxiety states and other neuroses; Enovid, the new synthetic steroid for the treatment of various menstrual

disorders; Zanolol, a new biliary abstergent; Nilevar, the new anabolic agent, and Rolicton, a new safe, nonmercurial oral diuretic. Also featured, will be Vallestiril, the new synthetic estrogen with extremely low incidence of side reactions; Pro-Banthine and Pro-Banthine with Dartal, the standards in anticholinergic therapy; and Dramamine and Dramamine-D, for the prevention and treatment of motion sickness and other nauseas.

Smith Kline & French Laboratories, Philadelphia, Pa. (Booth 40)

will feature: Mio-Pressin, a balanced combination of 3 antihypertensive agents (rauwolfia, protoveratrine and Dibenzylamine) that assure broad clinical usefulness and minimal side effects in the treatment of moderately severe to severe hypertension; and Spansule brand sustained release medication. With each Spansule preparation, a therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours.

United States Catheter & Instrument Corp., Glens Falls, N.Y. (Booth 46).

Specialists in the manufacture of cardiac catheters, electrodes and tubings. Manufacturer of a complete line of woven and knitted Teflon prostheses. A research engineer, well versed in design and production of cardiac catheters, will discuss problems, ideas, new developments, etc., at their booth.

Walker Laboratories, Inc., Mount Vernon, N. Y. (Booth 22).

Hedulin, the well-known oral anticoagulant will be featured at their booth, along with Nicotinic Acid 500 mg., for the treatment of hypercholesterolemia. Hedulin is prescribed as an anticoagulant of choice, because of its safety, predictability and uniformity of action. Large doses of Nicotinic Acid have proved effective in the reduction of elevated blood cholesterol levels.

Wallace Laboratories, New Brunswick, N. J. (Booth 50).

Their representatives look forward to discussing Miltrate, a new treatment for angina, with you. The drug consists of 200 mg. of Miltown plus 10 mg. of PETN, providing a new dovetailed therapy and preventing both cause and fear of angina. Miltrate has been proven safe for long-term use.

Warner-Chilcott Laboratories, Morris Plains, N. J. (Booth 81)

will feature Peritrate. Painful seizures often create fear in the patient with angina pectoris. Attacks can be controlled and fear arrested by prophylactic management with Peritrate, a long-acting coronary vasodilator. Pre-

scribed on a regular daily dosage schedule, Peritrate increases coronary circulation and lessens the frequency and severity of attacks. In addition, nitroglycerin dependence is often reduced and exercise tolerance increased. Peritrate with Phenobarbital is a product particularly designed for the tense, anxiety-prone angina patient.

Waters Corporation, Rochester, Minn. (Booth 17). Featured will be the new XC-100A densitometer for dye curve recording in cardiac research and diagnosis using the Fox green dye. Also oximeters, photographic recorders, nitrogen gas analyzer, cardiometer and thermistor with extrasensitive, fast probes.

Wesson Oil, New York, N. Y. (Booth 84) will exhibit a gas chromatogram, indicating the composition of cottonseed oil with a descriptive text and research findings in polyunsaturated fats. The product will be displayed and literature will be available.

Winthrop Laboratories, New York, N. Y. (Booth 45). Levophed, the natural antishock pressor hormone for patients in severe shock due to myocardial infarction. Levophed raises blood pressure within seconds. Unlike other agents, it also produces an increase in coronary blood flow and oxygen supply to the myocardium.

Wyeth Laboratories, Philadelphia, Pa. (Booth 21) will feature Equanitrate to break the pain-anxiety pain cycle of angina pectoris. It provides pro-

longed coronary vasodilatation, controls apprehension, anxiety and tension, reduces the number and severity of anginal attacks, and increases exercise tolerance. Also featured will be Bicillin; a single injection provides a full month's protection against attacks of rheumatic fever.

Wynn Pharmacal Corporation, Philadelphia, Pa. (Booth 49). Information, samples and reprints will be available on Quinaglute Dura-Tab S.M., the only oral sustained medication quinidine gluconate. Because of greater solubility, quinidine gluconate has been found to be better absorbed and tolerated than quinidine sulfate. In its sustained medication dosage, Quinaglute maintains uniform plasma levels up to 12 hours, and thus eliminates the valleys in plasma concentration during which arrhythmias tend to recur. The b.i.d. maintenance dosage schedule insures patient cooperation and convenience. It is indicated in cardiac arrhythmias, such as premature contractions, auricular tachycardia, flutter, fibrillation.

Year Book Publishers, Inc., Chicago, Ill. (Booth 20). Of special interest at their booth will be the New Second Edition of Kjellberg's *Diagnosis of Congenital Heart Disease*, Fourth Edition of Lipman & Massie's *Clinical Scalar Electrocardiography*, Ravin's *Auscultation of the Heart*, Matousek's *Manual of Differential Diagnosis*, New Year Book of Medicine, and Davis' *Radicular Syndromes with Emphasis on Chest Pain Simulating Coronary Disease*. Your inspection will be most welcome.

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ANNUAL DINNER, AMERICAN HEART ASSOCIATION

Sunday evening, October 25

ASSEMBLY PANEL MEETINGS

Monday, October 26

**ANNUAL MEETING OF THE ASSEMBLY OF THE
AMERICAN HEART ASSOCIATION**

Tuesday, October 27

ASSEMBLY LUNCHEON

Tuesday, October 27

The above events take place at the Bellevue Stratford Hotel

ANNUAL MEETING STAFF CONFERENCE OF HEART ASSOCIATIONS

Thursday evening, October 22 through Saturday, October 24

At the Warwick Hotel

ADMISSION REQUIREMENTS

For admission to sessions and exhibits, every participant is required to wear a badge:

White—Physician or Scientist

Yellow—Nonmedical Registrant

Green—Medical Student or Registered Nurse

Salmon—Staff of Heart Associations